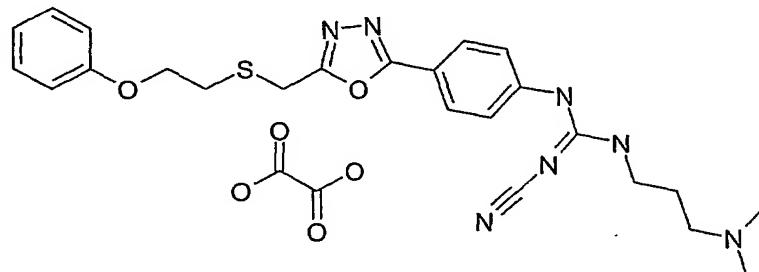


afford a yellow oil that solidified on standing. The solid was triturated with diethyl ether to afford the corresponding carbamimidic acid phenyl ester (1.78 g, 62% yield) as a yellow solid (MS for carbamimidic acid phenyl ester (ES^+) m/e 470). *N,N*-dimethylethylenediamine (1.87 g, 21.2 mmol, 20 eq.) was added to a solution of this 5 carbamimidic acid phenyl ester (0.50 g, 1.06 mmol, 1 eq.) in isopropanol, then heated to reflux. After 5 h, the reaction was cooled, diluted with ethyl acetate, and washed with aqueous sodium bicarbonate. The organic layer was collected, dried over MgSO_4 , filtered, and the solvent removed *in vacuo* to afford an orange oil. The oil was purified by silica gel flash chromatography using 10% 2M NH_3 in methanol in diethyl ether as the 10 mobile phase to afford 0.14 g (29%) of *N*-(2-dimethylamino-ethyl)-*N'*-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-cyanoguanidine as an off-white solid. The free base was converted to the oxalate salt by adding 1.1 eq. of oxalic acid 15 (0.03 g) in acetone to an acetone solution of the base to afford 0.13 g of *N*-(2-dimethylamino-ethyl)-*N'*-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-cyanoguanidine oxalate as a tan solid.

^1H NMR (DMSO-d6) δ 10.04 (s, 1H), 7.93 (m, 3H), 7.48 (d, 2H, $J=9$ Hz), 7.27 (m, 2H), 6.93 (m, 3H), 4.19 (m, 4H), 3.02 (m, 4H), 2.81 (t, 2H, $J=7$ Hz), 2.73 (s, 6H). IR (KBr, cm^{-1}) 3404, 3302, 3040, 2174, 1720, 1618, 1598, 1562, 1500, 1461, 1243, 1010. MS (ES^+) m/e 466. MS (ES^-) m/e 464. Anal. Calcd for $\text{C}_{25}\text{H}_{29}\text{N}_7\text{O}_6\text{S}$ C, 54.04; H, 5.26; 20 N, 17.65. Found C, 51.71; H, 5.70; N, 14.23. Analytical HPLC 95.7% purity. MP. softening at 138°C then decomposition at 145-147°C.

Example 120

Preparation of *N*-(3-dimethylamino-propyl)-*N'*-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-cyanoguanidine oxalate 25



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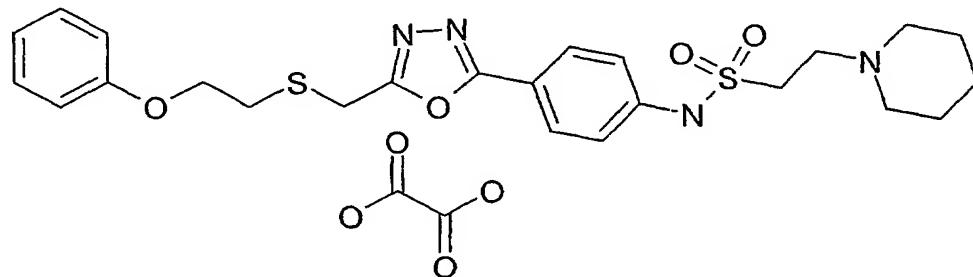
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 119, from the carbamimidic acid phenyl ester (1.2 g, 2.54 mmol, 1 eq.) and 3-dimethylaminopropylamine (5.19 g, 50.8 mmol, 20 eq.) to afford 0.22 g (18%) of *N*-(3-dimethylamino-propyl)-*N'*-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-cyanoguanidine as an off-white solid. The free base was converted to the oxalate salt as described to afford 0.20 g of *N*-(3-dimethylamino-propyl)-*N'*-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-cyanoguanidine oxalate as a white solid.

¹H NMR (DMSO-d₆) δ 9.78 (s, 1H), 7.92 (m, 3H), 7.47 (d, 2H, J=9 Hz), 7.28 (m, 2H), 6.93 (m, 3H), 4.20 (m, 4H), 3.33 (m, 2H), 3.02 (m, 4H), 2.73 (s, 6H), 1.88 (m, 2H). IR (KBr, cm⁻¹) 3316, 3255, 2171, 1720, 1600, 1500, 1237, 755, 720. MS (ES⁺) m/e 480. MS (ES⁻) m/e 478. Anal. Calcd for C₂₆H₃₁N₇O₆S C, 54.82; H, 5.49; N, 17.21. Found C, 53.91; H, 5.43; N, 16.76. Analytical HPLC 100% purity. MP softening at 110°C then decomposition from 130-134°C.

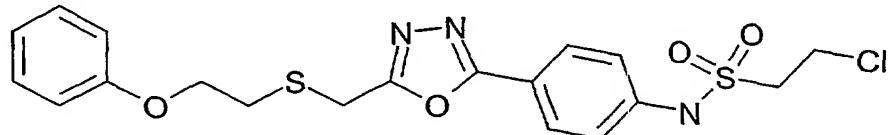
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Example 121

Preparation of 2-piperidin-1-yl-ethanesulfonic acid {4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-amide oxalate



20 a) Preparation of 2-chloro-ethanesulfonic acid {4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-amide

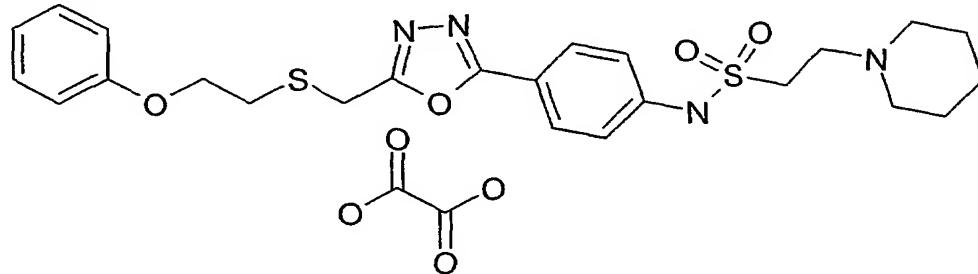


A solution of 4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenylamine (3.0 g, 9.16 mmol, 1 eq.) in anhydrous CH₂Cl₂ was treated with

triethylamine (1.39 g, 13.74 mmol, 1.5 eq.) and 2-chloro-1-ethanesulfonyl chloride (1.79 g, 10.99 mmol, 1.2 eq.). The reaction was allowed to stir at room temperature for 16 h, then was quenched with water and the organic layer removed. The aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated to afford an orange oil. The oil was purified by silica gel flash chromatography using a step gradient of ethyl acetate in hexane as the mobile phase to afford 0.97 g (23%) of 2-chloro-ethanesulfonic acid {4-[5-(2-phenoxy-ethylsulfonylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-amide as an off-white solid.

¹H NMR (DMSO-d6) δ 8.06 (d, 2H, J=8 Hz), 7.57 (d, 2H, J=9 Hz), 7.28 (m, 3H), 6.91 (m, 3H), 6.44 and 6.41 (m, 2H total), 6.32 and 6.27 (m, 2H total), 4.25 (s, 2H), 4.18 (t, 2H, J=7 Hz), 3.03 (t, 2H, J=7 Hz). IR (CHCl₃, cm⁻¹) 1602, 1491, 1384, 1217, 1163, 916. MS (ES⁻) m/e 416 [M-Cl]⁻. Anal. Calcd for C₁₉H₂₀ClN₃O₄S C, 50.27; H, 4.44; N, 9.26. Found C, 49.71; H, 4.15; N, 8.27.

b) Preparation of 2-piperidin-1-yl-ethanesulfonic acid {4-[5-(2-phenoxy-ethylsulfonylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-amide oxalate



2-Chloro-ethanesulfonic acid {4-[5-(2-phenoxy-ethylsulfonylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-amide (0.91 g, 2.0 mmol, 1 eq.) in anhydrous DMF was treated with sodium bicarbonate (0.50 g, 6.0 mmol, 3 eq.) and sodium iodide (0.03 g, 0.2 mmol, 0.1 eq.) followed by piperidine (0.51 g, 6.0 mmol, 3 eq.). The reaction was then heated to 90°C and allowed to stir at that temperature for 16 h. The reaction was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over MgSO₄, filtered, and the solvent removed in vacuo leaving an orange oil which was purified by silica gel flash chromatography using 10% 2M NH₃ in methanol in diethyl ether as the mobile phase to afford 0.95 g (94%) of 2-piperidin-1-yl-ethanesulfonic acid {4-[5-(2-phenoxy-ethylsulfonylmethyl)-

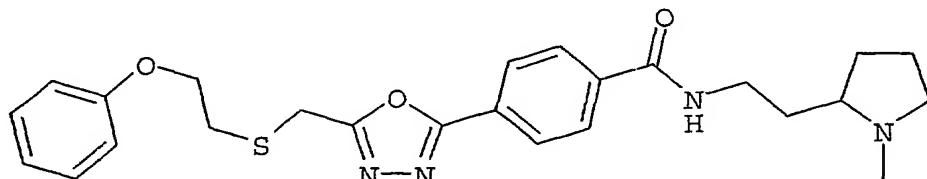
-252-

[1,3,4]oxadiazol-2-yl]-phenyl}-amide as a yellow oil. The free base was converted to the oxalate salt by adding 1.1 eq. of oxalic acid (0.19 g) in acetone dropwise to an acetone solution of the free base. The resulting white precipitate was collected by filtration and crystallized from methanol to afford 0.48 g of 2-piperidin-1-yl-ethanesulfonic acid {4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-amide oxalate as a 5 crystalline white solid.

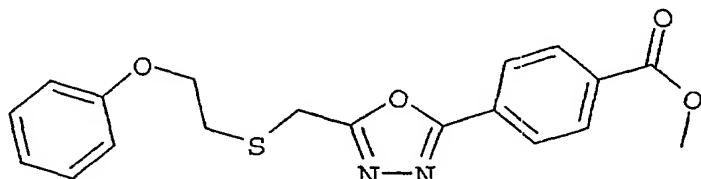
1H NMR (DMSO-d6) δ 7.93 (d, 2H, J=9 Hz), 7.39 (d, 2H, J=9 Hz), 7.27 (m, 2H), 6.93 (m, 3H), 4.19 (m, 4H), 3.62 (m, 2H), 3.14 (m, 2H), 3.02 (t, 2H, J=7 Hz), 2.82 (m, 4H), 1.57 (m, 4H), 1.41 (m, 2H). IR (KBr, cm-1) 3409, 1617, 1344, 1243, 1159, 916, 10 759, 705. MS (ES+) m/e 503. MS (ES-) m/e 501. Anal. Calcd for C₂₆H₃₂N₄O₈S₂ C, 52.69; H, 5.44; N, 9.45. Found C, 52.44; H, 5.46; N, 9.37. Analytical HPLC 99.6% purity. MP softening at 159°C then 162-166 °C.

Example 122

15 Preparation of 2-{[(2-phenoxyethyl)thio]methyl}-5-{4-[(2-(N-methylpyrrolidin-2-yl)ethyl)amino]carbonyl}phenyl]-1,3,4-oxadiazole



a) 2-{[(2-Phenoxyethyl)thio]methyl}-5-[4-(methoxycarbonyl)phenyl]-1,3,4-oxadiazole



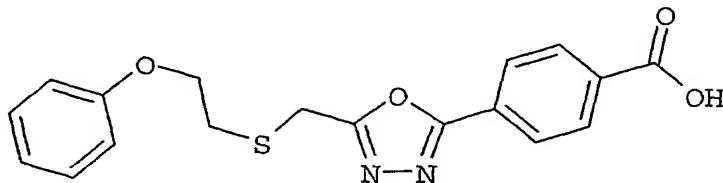
20 A solution of 2-{[(2-phenoxyethyl)thio]acetic acid hydrazide hydrochloride (3.15 g, 12 mmol), triethylamine (4.2 mL, 30 mmol) and terephthalic acid monomethyl ester chloride (1.99 g, 10 mmol) in methylene chloride (100 mL) was stirred at room temperature for 3 h. After filtering the solids, the filtrate was concentrated. The residue was recrystallized from ethanol to yield a pale yellow solid (1.31 g, 3.37 mmol). This solid, 4-(dimethylamino)phenyldiphenylphosphine (2.06 g, 6.74 mmol), triethylamine (1.4

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mL, 10 mmol) and carbon tetrachloride (1.6 mL, 16.6 mmol) were stirred in acetonitrile (75 mL) at room temperature for 18 h. The product was filtered from the reaction mixture, washed with acetonitrile (50 mL) and dried to yield 1.13 g (30%) of a pale yellow solid, which was used without further purification.

5 ¹H NMR (CDCl₃) δ 8.14 (d, 2H, J=9 Hz), 8.06 (d, 2H, J=9 Hz), 7.23 (m, 2H), 6.92 (dd, 1H, J=7 and 8 Hz), 6.86 (d, 2H, J=8 Hz), 4.19 (t, 2H, J=12 Hz), 4.05 (s, 2H), 3.93 (s, 3H), 3.03 (t, 2H, J=12 Hz). MS (ES+) m/e 371 (M+1).

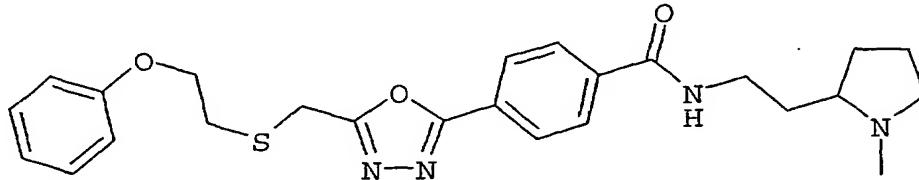
10 b) 2-{{(2-Phenoxyethyl)thio}methyl}-5-[4-(hydroxycarbonyl)phenyl]-1,3,4-oxadiazole



A mixture of 2-{{(2-phenoxyethyl)thio}methyl}-5-[4-(methoxycarbonyl)phenyl]-1,3,4-oxadiazole (1.13 g, 3.0 mmol) and 2N aqueous NaOH (4.5 mL, 9.0 mmol) in THF (20 mL) was stirred at room temperature for 16 h. The mixture was diluted with water (30 mL) and extracted with ethyl ether (50 mL). The aqueous material was acidified with 2N HCl to a pH of 5, then extracted with ethyl ether (3x30 mL). The organic material was dried (MgSO₄), filtered and concentrated to yield 803 mg (74%) of a pale yellow solid.

15 ¹H NMR (CDCl₃) δ 8.20 (d, 2H, J=8 Hz), 8.12 (d, 2H, J=8 Hz), 7.25 (m, 2H), 6.93 (dd, 1H, J=7 and 8 Hz), 6.87 (d, 2H, J=8 Hz), 4.20 (t, 2H, J=12 Hz), 4.08 (s, 2H), 3.05 (t, 2H, J=12 Hz). MS (ES-) m/e 355 (M-1).

c) 2-{{(2-Phenoxyethyl)thio}methyl}-5-{4-[((2-(N-methyl pyrrolidin-2-yl)ethyl)amino)carbonyl]phenyl}-1,3,4-oxadiazole



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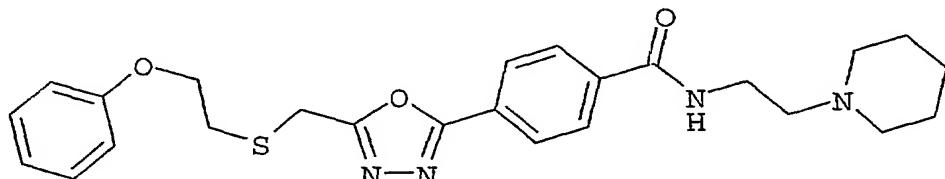
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A solution of 2-[(2-phenoxyethyl)thio]methyl]-5-[4-(hydroxycarbonyl)phenyl]-1,3,4-oxadiazole (300 mg, 0.84 mmol), 2-(2-aminoethyl)-1-methylpyrrolidine (0.18 mL, 1.24 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (242 mg, 1.26 mmol) and 1-hydroxybenzo-triazole (171 mg, 1.26 mmol) in N,N-dimethylformamide (10 mL) was stirred at room temperature for 16 h. The mixture was diluted with ethyl acetate (50 mL) and extracted with saturated aqueous lithium chloride (2x25 mL), dried (MgSO_4), filtered and concentrated to yield 700 mg of a yellow oil. This oil was purified by preparative TLC [90% methylend chloride-5% methanol-5%(2.0 N ammonia in methanol)] to yield 146 mg (37%) of a white solid.

¹H NMR (CDCl_3) δ 8.75 (br s, 1H), 8.07 (d, 2H, $J=8$ Hz), 7.88 (d, 2H, $J=8$ Hz), 7.24 (m, 2H), 6.93 (dd, 1H, $J=7$ and 8 Hz), 6.87 (d, 2H, $J=8$ Hz), 4.19 (t, 2H, $J=12$ Hz), 4.05 (s, 2H), 3.77 (m, 1H), 3.47 (m, 1H), 3.15 (m, 1H), 3.04 (t, 2H, $J=12$ Hz), 2.57 (m, 1H), 2.40 (s, 3H), 2.31 (m, 1H), 1.90 (m, 2H), 1.75 (m, 4H). IR (film, cm^{-1}) 3432, 3335, 2943, 2868, 2778, 2359, 1641, 1584, 1547, 1493, 1456, 1302, 1244, 1082, 1021, 863, 753, 694, 654. MS (ES+) m/e 467 (M+1). Anal. Calcd for $\text{C}_{31}\text{H}_{33}\text{N}_3\text{O}_2\text{S}$: C, 64.35; H, 6.48; N, 12.01; S, 6.87. Found C, 64.42; H, 6.19; N, 12.45; S, 6.80.

Example 123

Preparation of 2-[(2-phenoxyethyl)thio]methyl]-5-{4-[(2-piperidinoethyl)amino]carbonyl}phenyl]-1,3,4-oxadiazole



This compound was synthesized similarly to 2-[(2-Phenoxyethyl)thio]methyl]-5-{4-[(2-(N-methyl pyrrolidin-2-yl)ethyl)amino]carbonyl}phenyl]-1,3,4-oxadiazole using 1-(2-aminoethyl)piperidine (0.12 mL).

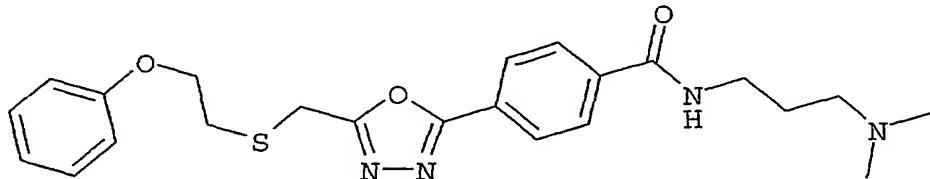
¹H NMR (CDCl_3) δ 8.08 (d, 2H, $J=9$ Hz), 7.89 (d, 2H, $J=9$ Hz), 7.24 (m, 2H), 7.15 (br s, 1H), 6.93 (dd, 1H, $J=7$ and 8 Hz), 6.87 (d, 2H, $J=9$ Hz), 4.20 (t, 2H, $J=12$ Hz), 4.06 (s, 2H), 3.53 (dd, 2H, $J=6$ and 11 Hz), 3.04 (t, 2H, $J=12$ Hz), 2.57 (dd, 2H, $J=6$ and 11 Hz), 2.44 (m, 4H), 1.60 (m, 4H), 1.47 (m, 2H). IR (film, cm^{-1}) 3313, 2938, 2885, 2851, 2778, 1635, 1552, 1493, 1296, 1239, 1024, 747. MS (ES+) m/e 467 (M+1). Anal. Calcd

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for C₂₅H₃₀N₄O₃S: C, 64.35; H, 6.48; N, 12.01; S, 6.87. Found C, 64.02; H, 6.41; N, 12.00; S, 7.02.

Example 124

- 5 Preparation of 2-{[(2-phenoxyethyl)thio]methyl}-5-{4-[(N',N'-dimethyl-1,3-propanediamino)carbonyl]phenyl}-1,3,4-oxadiazole

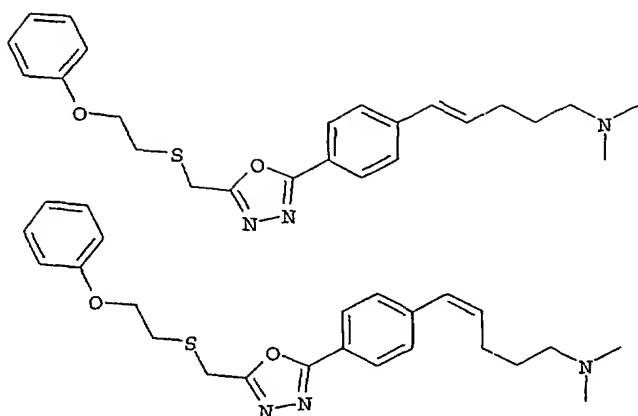


This compound was synthesized similarly to 2-{[(2-Phenoxyethyl)thio]methyl}-5-{4-[(2-(N-methyl pyrrolidin-2-yl)ethyl)amino)carbonyl]phenyl}-1,3,4-oxadiazole using
10 3-(dimethylamino)propylamine (0.11 mL).

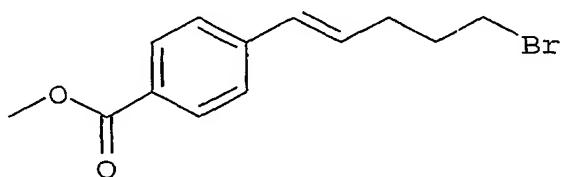
¹H NMR (CDCl₃) δ 8.81 (br s, 1H), 8.07 (d, 2H, J=8 Hz), 7.87 (d, 2H, J=8 Hz),
7.24 (m, 2H), 6.93 (dd, 1H, J=7 and 8 Hz), 6.87 (d, 2H, J=8 Hz), 4.20 (t, 2H, J=12 Hz),
4.05 (s, 2H), 3.58 (dd, 2H, J=6 and 11 Hz), 3.04 (t, 2H, J=12 Hz), 2.54 (dd, 2H, J=6 and
11 Hz), 2.30 (s, 6H), 1.77 (m, 2H). IR (film, cm⁻¹) 3431, 3345, 2943, 2867, 2810, 2762,
15 1641, 1581, 1542, 1494, 1466, 1300, 1246, 1178, 1082, 1026, 750, 693, 651. MS (ES+)
m/e 441 (M+1). Anal. Calcd for C₂₃H₂₈N₄O₃S: C, 62.70; H, 6.41; N, 12.72; S, 7.28.
Found C, 62.13; H, 6.32; N, 12.63; S, 6.99.

Example 125

- 20 Preparation of 2-{[(2-Phenoxyethyl)thio]methyl}-5-{4-[5-(N,N-dimethylamino)penten-1-yl]phenyl}-1,3,4-oxadiazole, (E)- and (Z)-isomers



a) Methyl 4-(5-bromopenten-1-yl)benzoate



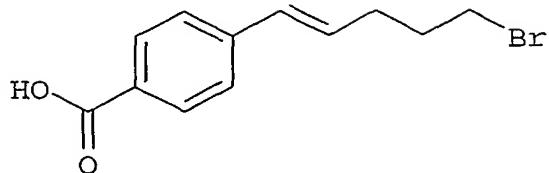
A mixture of methyl 4-formylbenzoate (9.85 g, 60 mmol), 4-bromobutyltriphenylphosphonium bromide (31.56 g, 66 mmol), powdered NaOH (3 g, 75 mmol), and 12 drops of water in methylene chloride (150 mL) was stirred under reflux for 4 h. The mixture was allowed to cool to room temperature and filtered. The filtrate was concentrated and chromatographed on a silica gel column, eluted with ethyl acetate/hexanes 1:50 to 1:30, to give the Z-isomer (colorless oil, 3.68 g, 22%), a mixture of Z- and E-isomers (colorless oil, 2.69 g, 16%), and the E-isomer (white solid, 2.97 g, 17%).

E-isomer: ^1H NMR (CDCl_3) δ 7.94 (d, 2H, $J=8.5$ Hz), 7.37 (d, 2H, $J=8.4$ Hz), 6.46 (d, 1H, $J=15.8$ Hz), 6.28 (dt, 1H, $J=15.8, 7.0$ Hz), 3.88 (s, 3H), 3.44 (t, 2H, $J=6.6$ Hz), 2.39 (q, 2H, $J=7.0$ Hz), 2.03 (quint, 2H, 6.6 Hz). MS (ES+) m/e 284 (M+1).

Z-isomer: ^1H NMR (CDCl_3) δ 7.98 (d, 2H, $J=8.1$ Hz), 7.31 (d, 2H, $J=8.4$ Hz), 6.48 (d, 1H, $J=11.7$ Hz), 5.70 (dt, 1H, $J=11.7, 7.3$ Hz), 3.89 (s, 3H), 3.39 (t, 2H, $J=6.8$ Hz), 2.47 (q, 2H, $J=7.3$ Hz), 1.99 (quint, 2H, 6.9 Hz). MS (ES+) m/e 284 (M+1).

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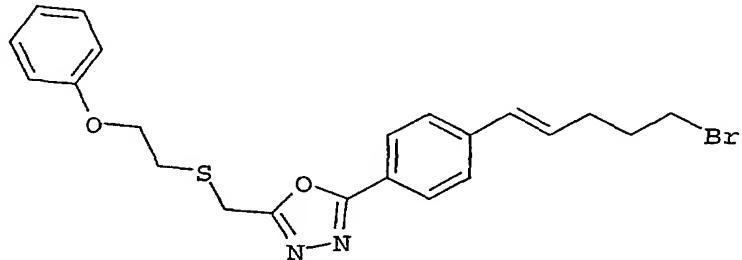
b) 4-(5-bromopenten-1-yl)benzoic acid



Methyl 4-(5-bromopenten-1-yl)benzoate (1.415 g, 5 mmol) was dissolved in 1,4-dioxane (25 mL) and 2 N NaOH (25 mL, 50 mmol) was added. The mixture was stirred 5 at room temperature for 5 h, cooled in an ice bath, acidified with conc. HCl, and extracted with ether (3 x 25 mL). The combined ether extracts were dried (MgSO_4) and concentrated to give a white solid (1.264, 94%).

E-isomer: ^1H NMR (CDCl_3) δ 8.05 (d, 2H, $J=7.7$ Hz), 7.43 (d, 2H, $J=8.5$ Hz), 6.51 (d, 1H, $J=16.3$ Hz), 6.34 (dt, 1H, $J=16.3, 6.9$ Hz), 3.47 (t, 2H, $J=6.9$ Hz), 2.43 (q, 2H, 10 $J=6.9$ Hz), 2.07 (quint, 2H, 6.8 Hz). MS (ES-) m/e 268 (M-1).

c) 2-{{[(2-Phenoxyethyl)thio]methyl}-5-[4-(5-bromopenten-1-yl)phenyl]-1,3,4-oxadiazole

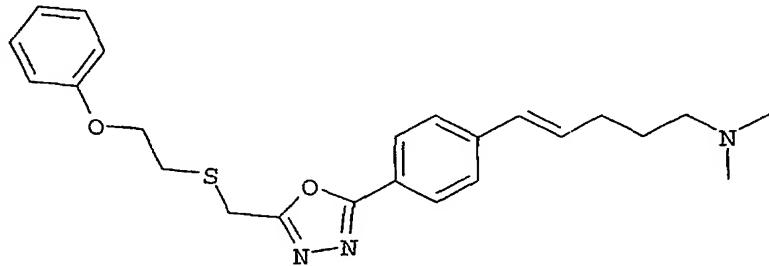


A stirred mixture of 4-(5-bromopenten-1-yl)benzoic acid (1.264 g, 4.7 mmol), 2-(2-phenoxyethyl)thioacetylhydrazide hydrochloride (1.314 g, 5 mmol), and 4-(N,N-dimethylamino)phenyldiphenylphosphine (4.58 g, 15 mmol) in acetonitrile (50 mL) was cooled in ice bath and triethylamine (3.04 g, 30 mmol) in carbon tetrachloride (3.85 g, 25 mmol) was added dropwise. The cooling bath was removed after 10 min and stirring was 20 continued for 5 h. The mixture was concentrated to approximately half the original volume and partitioned between ether (150 mL) and 2 N HCl (150 mL). The ether layer was washed with 2 N HCl (4 x 50 mL), dried (MgSO_4), and concentrated. The residue was purified by chromatography (SiO_2 , ethyl acetate/hexanes 1:5) to give a white solid (1.43 g, 66%).

E-isomer: ^1H NMR (CDCl_3) δ 7.96 (d, 2H, $J=8.5$ Hz), 7.45 (d, 2H, $J=8.5$ Hz), 7.27 (m, 2H), 6.96 (t, 1H, $J=7.7$ Hz), 6.90 (d, 2H, $J=8.5$ Hz), 6.50 (d, 1H, $J=16.2$ Hz), 6.32 (dt, 1H, $J=16.2, 6.9$ Hz), 4.22 (t, 2H, $J=6.0$ Hz), 4.06 (s, 2H), 3.47 (t, 2H, $J=6.9$ Hz), 3.06 (t, 2H, $J=6.0$ Hz), 2.43 (q, 2H, $J=6.9$ Hz), 2.07 (quint, 2H, 6.9 Hz). MS (ES+) m/e 460 (M+1).

Z-isomer: ^1H NMR (CDCl_3) δ 7.97 (d, 2H, $J=8.5$ Hz), 7.37 (d, 2H, $J=8.5$ Hz), 7.22~7.26 (m, 2H), 6.93 (t, 1H, $J=7.3$ Hz), 6.87 (d, 2H, $J=7.7$ Hz), 6.48 (d, 1H, $J=11.8$ Hz), 5.72 (dt, 1H, $J=11.7, 7.3$ Hz), 4.19 (t, 2H, $J=6.2$ Hz), 4.04 (s, 2H), 3.41 (t, 2H, $J=6.6$ Hz), 3.04 (t, 2H, $J=6.2$ Hz), 2.49 (q, 2H, $J=7.3$ Hz), 2.01 (quint, 2H, 7.0 Hz). MS (ES+) m/e 460 (M+1).

d) 2-{{(2-Phenoxyethyl)thio}methyl}-5-{4-[5-(N,N-dimethylamino)penten-1-yl]phenyl}-1,3,4-oxadiazole



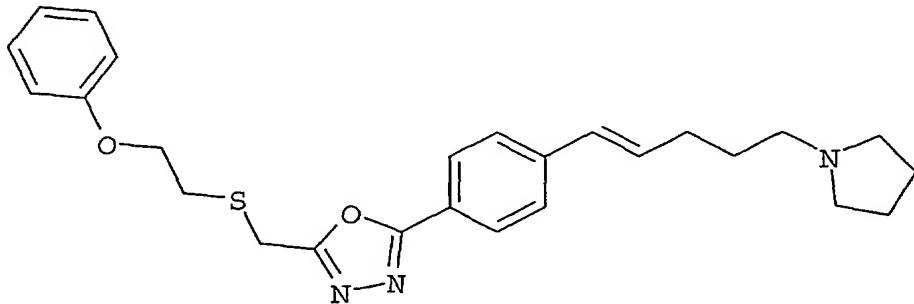
A mixture of 2-{{(2-phenoxyethyl)thio}methyl}-5-{4-(5-bromopenten-1-yl)phenyl}-1,3,4-oxadiazole (300 mg, 0.65 mmol), 2 N dimethylamine in tetrahydrofuran (1.7 mL, 3.4 mmol), and potassium carbonate (903 mg, 6.5 mmol) in acetonitrile (5 mL) was stirred at room temperature for 24 h, diluted with methylene chloride (25 mL) and filtered. The filtrate was concentrated and purified by chromatography (silica gel, methanol/methylene chloride 2% to 10%) to give a white solid (263 mg, 96%).

E-isomer: ^1H NMR (CDCl_3) δ 7.93 (d, 2H, $J=8.5$ Hz), 7.42 (d, 2H, $J=8.4$ Hz), 7.22~7.27 (m, 2H), 6.93 (t, 1H, $J=7.3$ Hz), 6.87 (d, 2H, $J=7.7$ Hz), 6.42 (d, 1H, $J=16.1$ Hz), 6.34 (dt, 1H, $J=15.7, 6.4$ Hz), 4.19 (t, 2H, $J=6.2$ Hz), 4.03 (s, 2H), 3.03 (t, 2H, $J=6.2$ Hz), 2.40 (m, 2H), 2.30 (s, 6H), 2.27 (m, 2H), 1.71 (quint, 2H, 7.3 Hz). IR (KBr, cm^{-1}) 3074, 3056, 3038, 2955, 2924, 2856, 1602, 1495, 1237, 1168, 751. MS (ES+) m/e 424 (M+1). Anal. Calcd for $\text{C}_{24}\text{H}_{29}\text{N}_3\text{O}_2\text{S}$: C, 68.05; H, 6.90; N, 9.92; S, 7.57. Found C, 68.16; H, 6.99; N, 10.23; S, 7.66.

Z-isomer: ^1H NMR (CDCl_3) δ 7.96 (d, 2H, $J=8.4$ Hz), 7.37 (d, 2H, $J=8.4$ Hz), 7.22~7.26 (m, 2H), 6.92 (t, 1H, $J=7.3$ Hz), 6.87 (d, 2H, $J=8.0$ Hz), 6.44 (d, 1H, $J=11.8$ Hz), 5.75 (dt, 1H, $J=11.4$, 7.3 Hz), 4.19 (t, 2H, $J=6.2$ Hz), 4.03 (s, 2H), 3.04 (t, 2H, $J=6.2$ Hz), 2.32~2.39 (m, 4H), 2.29 (s, 6H), 1.69 (quint, 2H, 7.3 Hz). IR (KBr, cm^{-1}) 3029, 5 2940, 2863, 2844, 2649, 1598, 1505, 1246, 1174, 752. MS (ES+) m/e 424 (M+1). Anal. Calcd for $\text{C}_{24}\text{H}_{29}\text{N}_3\text{O}_2\text{S}$: C, 68.05; H, 6.90; N, 9.92; S, 7.57. Found C, 68.45; H, 6.44; N, 10.37; S, 7.41.

Example 126

10 Preparation of 2-{{(2-Phenoxyethyl)thio)methyl}-5-[4-(5-pyrrolidinopenten-1-yl)phenyl]-1,3,4-oxadiazole

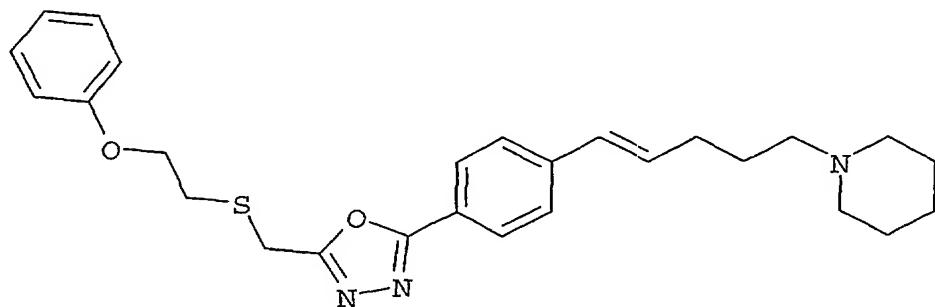


A mixture of 2-{{(2-phenoxyethyl)thio)methyl}-5-[4-(5-bromopenten-1-yl)phenyl]-1,3,4-oxadiazole (150 mg, 0.33 mmol), pyrrolidine (118 mg, 1.65 mmol), and 15 potassium carbonate (457 mg, 3.3 mmol) in acetonitrile (3.5 mL) was stirred at room temperature for 24 h, diluted with methylene chloride (15 mL), filtered, dried (MgSO_4), and concentrated. The residue was purified by preparative TLC (silica gel, 10% methanol/methylene chloride) to give a yellow oil (129 mg, 87%).

1 ^1H NMR (CDCl_3) δ 7.92 (d, 2H, $J=8.4$ Hz), 7.42 (d, 2H, $J=8.4$ Hz), 7.22~7.26 (m, 2H), 6.93 (t, 1H, $J=7.7$ Hz), 6.87 (d, 2H, $J=7.7$ Hz), 6.41 (d, 1H, $J=15.7$ Hz), 6.36 (dt, 1H, $J=15.7$, 6.5 Hz), 4.19 (t, 2H, $J=6.2$ Hz), 4.03 (s, 2H), 3.03 (t, 2H, $J=6.2$ Hz), 2.46~2.50 (m, 6H), 2.27 (q, 2H, $J=6.9$ Hz), 1.67~1.80 (m, 6H). IR (film, cm^{-1}) 3070, 3024, 2968, 2841, 2793, 1598, 1506, 1337, 1306, 1229, 1020, 736. MS (ES+) m/e 450 (M+1). Anal. Calcd for $\text{C}_{26}\text{H}_{31}\text{N}_3\text{O}_2\text{S}$: C, 69.46; H, 6.95; N, 9.35; S, 7.13. Found C, 68.98; H, 7.01; N, 25 9.73; S, 7.19.

Example 127

Preparation of 2-{{(2-Phenoxyethyl)thio}methyl}-5-[4-(5-piperidinopenten-1-yl)phenyl]-1,3,4-oxadiazole

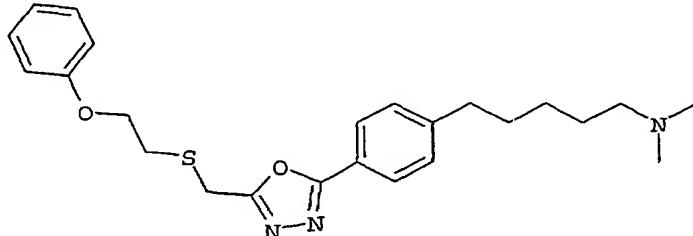


5 A mixture of 2-{{(2-phenoxyethyl)thio}methyl}-5-[4-(5-bromopenten-1-yl)phenyl]-1,3,4-oxadiazole (150 mg, 0.33 mmol), piperidine (140 mg, 1.65 mmol), and potassium carbonate (458 mg, 3.3 mmol) in acetonitrile (3.5 mL) was stirred at room temperature for 18 h, diluted with methylene chloride (15 mL), filtered, dried (MgSO_4), and concentrated. The residue was purified by preparative TLC (silica gel, 10%
10 methanol/methylene chloride) to give yellow oil (136 mg, 89%).

^1H NMR (CDCl_3) δ 7.92 (d, 2H, $J=8.5$ Hz), 7.42 (d, 2H, $J=8.4$ Hz), 7.22~7.26 (m, 2H), 6.93 (t, 1H, $J=7.3$ Hz), 6.87 (d, 2H, $J=8.4$ Hz), 6.41 (d, 1H, $J=16.1$ Hz), 6.34 (dt, 1H, $J=16.1$, 6.9 Hz), 4.19 (t, 2H, $J=6.2$ Hz), 4.03 (s, 2H), 3.03 (t, 2H, $J=6.2$ Hz), 2.38~2.43 (m, 6H), 2.25 (q, 2H, $J=6.9$ Hz), 1.43~1.74 (m, 8H). IR (film, cm^{-1}) 3072, 3027, 2945,
15 2936, 2691, 1600, 1533, 1274, 1196, 1020, 764. MS (ES+) m/e 464 (M+1). Anal. Calcd for $\text{C}_{27}\text{H}_{33}\text{N}_3\text{O}_2\text{S}$: C, 69.95; H, 7.17; N, 9.06; S, 6.92. Found C, 69.24; H, 7.12; N, 9.68;
S, 7.11.

Example 128

Preparation of 2-{{(2-Phenoxyethyl)thio}methyl}-5-{4-[5-(N,N-dimethylamino)pentan-1-yl]phenyl}-1,3,4-oxadiazole
20



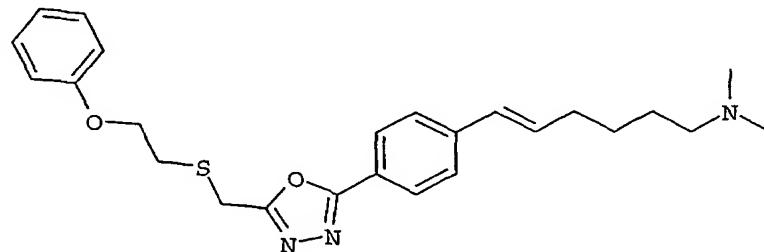
A mixture of (E)- and (Z)-2-{{[(2-phenoxyethyl)thio]methyl}-5-{4-[5-(N,N-dimethylamino)penten-1-yl]phenyl}-1,3,4-oxadiazole was made according to the above procedure from 460 mg (1 mmol) of a mixture of (E)- and (Z)-2-{{[(2-phenoxyethyl)thio]methyl}-5-[4-(5-bromopenten-1-yl)phenyl]-1,3,4-oxadiazole. Without 5 purification this material was stirred with p-toluenesulfonylhydrazide (2.25 g, 12 mmol) and sodium acetate trihydrate (1.02 g, 7.5 mmol) in tetrahydrofuran (12 mL) and water (12 mL) under reflux for 6 h. 2 N NaOH (20 mL) was added and the mixture was extracted with methylene chloride (2 x 20 mL). The combined methylene chloride extracts were dried (MgSO_4), and concentrated. The residue was purified by column 10 chromatography (silica gel, methanol/methylene chloride 2% to 5% to 10%) to give a colorless oil (333 mg, 78% over two steps).

¹H NMR (CDCl_3) δ 7.91 (d, 2H, $J=8.1$ Hz), 7.27 (d, 2H, $J=8.4$ Hz), 7.22~7.26 (m, 2H), 6.92 (t, 1H, $J=7.3$ Hz), 6.87 (d, 2H, $J=8.5$ Hz), 4.18 (t, 2H, $J=6.2$ Hz), 4.02 (s, 2H), 3.03 (t, 2H, $J=6.2$ Hz), 2.66 (t, 2H, $J=7.7$ Hz), 2.24 (t, 2H, $J=7.5$ Hz), 2.20 (s, 6H), 1.65 15 (quint, 2H, 7.7 Hz), 1.49 (q, 2H, $J=7.5$ Hz), 1.34 (q, 2H, $J=7.5$ Hz). IR (film, cm^{-1}) 3034, 3017, 2954, 2883, 2820, 1515, 1357, 1344, 1235, 1137, 1002. MS (ES+) m/e 426 (M+1). Anal. Calcd for $\text{C}_{24}\text{H}_{31}\text{N}_3\text{O}_2\text{S}$: C, 67.73; H, 7.34; N, 9.87; S, 7.53. Found C, 67.37; H, 7.42; N, 10.06; S, 7.27.

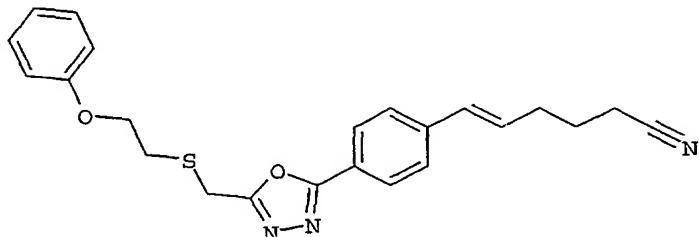
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Example 129

Preparation of 2-{{[(2-Phenoxyethyl)thio]methyl}-5-{4-[6-(N,N-dimethylamino)hexen-1-yl]phenyl}-1,3,4-oxadiazole



a) 2-{{(2-Phenoxyethyl)thio)methyl}-5-[4-(5-cyanopenten-1-yl)phenyl]-1,3,4-oxadiazole

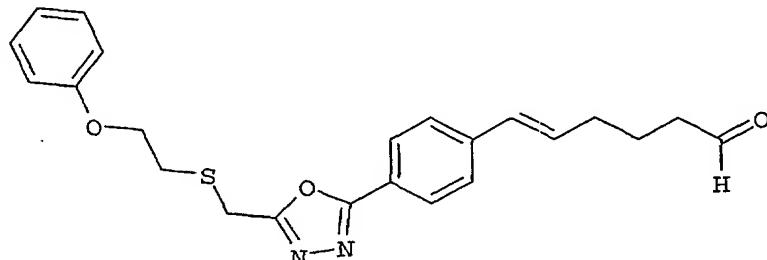


A mixture of 2-{{(2-phenoxyethyl)thio)methyl}-5-[4-(5-bromopenten-1-yl)phenyl]-1,3,4-oxadiazole (460 mg, 1 mmol) and potassium cyanide (195 mg, 3 mmol) in dimethylsulfoxide (6 mL) was stirred at room temperature for 4 h. Water (25 mL) was added and the mixture was extracted with ethyl acetate (3 x 15 mL). The combined ethyl acetate extracts were washed with water (3 x 15 mL) and brine (15 mL), dried (MgSO_4), and concentrated to give a pale yellow solid (403 mg, 100%).

E-isomer: ^1H NMR (CDCl_3) δ 7.97 (d, 2H, $J=7.7$ Hz), 7.46 (d, 2H, $J=7.7$ Hz), 7.28 (m, 2H), 6.96 (t, 1H, $J=7.3$ Hz), 6.90 (d, 2H, $J=7.3$ Hz), 6.51 (d, 1H, $J=15.4$ Hz), 6.29 (dt, 1H, $J=15.4, 7.7$ Hz), 4.22 (t, 2H, $J=6.0$ Hz), 4.06 (s, 2H), 3.06 (t, 2H, $J=6.0$ Hz), 2.41~2.46 (m, 4H), 1.89 (quint, 2H, 6.9 Hz). MS (ES+) m/e 406 (M+1).

Z-isomer: ^1H NMR (CDCl_3) δ 8.01 (d, 2H, $J=7.7$ Hz), 7.37 (d, 2H, $J=8.5$ Hz), 7.28 (m, 2H), 6.95 (t, 1H, $J=7.7$ Hz), 6.90 (d, 2H, $J=7.7$ Hz), 6.56 (d, 1H, $J=11.1$ Hz), 5.72 (dt, 1H, $J=11.1, 6.8$ Hz), 4.22 (t, 2H, $J=6.0$ Hz), 4.07 (s, 2H), 3.06 (t, 2H, $J=6.0$ Hz), 2.51 (m, 2H), 2.37 (t, 2H, $J=6.8$ Hz), 1.85 (m, 2H). MS (ES+) m/e 406 (M+1).

b) 2-{{(2-Phenoxyethyl)thio)methyl}-5-[4-(6-oxohexen-1-yl)phenyl]-1,3,4-oxadiazole



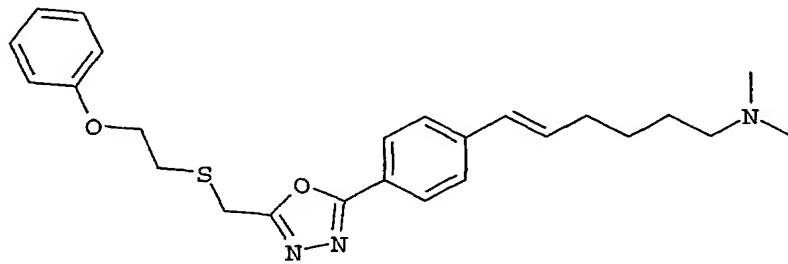
A solution of 2-{{(2-phenoxyethyl)thio)methyl}-5-[4-(5-cyanopenten-1-yl)phenyl]-1,3,4-oxadiazole (400 mg, 1 mmol) in methylene chloride (10 mL) was cooled to -78°C and 1 M DIBAL-H in hexane (2 mL, 2 mmol) was added dropwise. The

mixture was stirred at -78 °C for 2 h, 1 N HCl (20 mL) was added, and the mixture was allowed to warmed to room temperature. The mixture was extracted with methylene chloride (3 x 10 mL). The combined methylene chloride extracts were dried (MgSO_4), concentrated, and purified by chromatography (silica gel, ethyl acetate/hexanes 1:4) to give a white solid (146 mg, 36%).

E-isomer: ^1H NMR (CDCl_3) δ 9.81 (s, 1H), 7.96 (d, 2H, $J=7.7$ Hz), 7.45 (d, 2H, $J=8.6$ Hz), 7.28 (m, 2H), 6.96 (t, 1H, $J=7.7$ Hz), 6.90 (d, 2H, $J=7.7$ Hz), 6.45 (d, 1H, $J=16.3$ Hz), 6.33 (dt, 1H, $J=16.3, 6.8$ Hz), 4.22 (t, 2H, $J=6.0$ Hz), 4.06 (s, 2H), 3.06 (t, 2H, $J=6.0$ Hz), 2.53 (t, 2H, $J=6.0$ Hz), 2.31 (dd, 2H, $J=10.8, 7.7$ Hz), 1.86 (quint, 2H, 7.7 Hz). MS (ES+) m/e 412 (M+1).

Z-isomer: ^1H NMR (CDCl_3) δ 9.78 (s, 1H), 7.99 (d, 2H, $J=8.5$ Hz), 7.38 (d, 2H, $J=8.6$ Hz), 7.26~7.29 (m, 2H), 6.95 (t, 1H, $J=7.7$ Hz), 6.90 (d, 2H, $J=7.7$ Hz), 6.49 (d, 1H, $J=11.1$ Hz), 5.75 (dt, 1H, $J=11.1, 6.8$ Hz), 4.22 (t, 2H, $J=6.4$ Hz), 4.06 (s, 2H), 3.06 (t, 2H, $J=6.0$ Hz), 2.48 (t, 2H, $J=6.8$ Hz), 2.39 (m, 2H), 1.81 (m, 2H). MS (ES+) m/e 412 (M+1).

c) 2-{{(2-Phenoxyethyl)thio}methyl}-5-{4-[6-(N,N-dimethylamino)hexen-1-yl]phenyl}-1,3,4-oxadiazole



To a stirred mixture of 2-{{(2-phenoxyethyl)thio}methyl}-5-[4-(6-oxohexen-1-yl)phenyl]-1,3,4-oxadiazole (103 mg, 0.25 mmol), 2 M dimethylamine in tetrahydrofuran (0.25 mL, 0.5 mmol), and acetic acid (15 mg, 0.25 mmol) in 1,2-dichloroethane (2 mL) was added sodium triacetoxyborohydride (106 mg, 0.5 mmol) and stirring was continued at room temperature for 2 h. 2N NaOH (10 mL) was added and the mixture was extracted with methylene chloride (3 x 10 mL). The combined methylene chloride extracts were dried (MgSO_4), concentrated, and purified by preparative TLC (silica gel, 10% methanol/methylene chloride) to give a white solid (87 mg, 80%).

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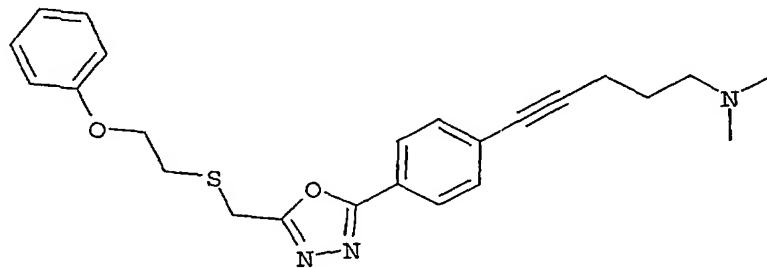
E-isomer: ^1H NMR (CDCl_3) δ 7.95 (d, 2H, $J=8.6$ Hz), 7.44 (d, 2H, $J=8.6$ Hz), 7.28 (m, 2H), 6.95 (t, 1H, $J=7.7$ Hz), 6.90 (d, 2H, $J=7.7$ Hz), 6.43 (d, 1H, $J=15.4$ Hz), 6.36 (dt, 1H, $J=15.4$, 6.8 Hz), 4.21 (t, 2H, $J=6.4$ Hz), 4.05 (s, 2H), 3.06 (t, 2H, $J=6.0$ Hz), 2.34 (t, 4H, $J=6.8$ Hz), 2.29 (s, 6H), 2.28(m, 2H), 1.50~1.59 (m, 4H). IR (KBr, cm^{-1}) 3070, 3035, 5 2954, 2879, 2684, 1599, 1566, 1475, 1339, 1254, 1057, 921, 748. MS (ES+) m/e 438 (M+1). Anal. Calcd for $\text{C}_{25}\text{H}_{31}\text{N}_3\text{O}_2\text{S}$: C, 68.62; H, 7.14; N, 9.60; S, 7.33. Found C, 68.33; H, 7.21; N, 9.47; S, 7.28.

Z-isomer: ^1H NMR (CDCl_3) δ 7.99 (d, 2H, $J=7.7$ Hz), 7.39 (d, 2H, $J=8.6$ Hz), 7.28 (m, 2H), 6.95 (t, 1H, $J=7.7$ Hz), 6.90 (d, 2H, $J=7.7$ Hz), 6.45 (d, 1H, $J=11.1$ Hz), 5.78 (dt, 1H, $J=11.1$, 7.7 Hz), 4.22 (t, 2H, $J=6.4$ Hz), 4.06 (s, 2H), 3.06 (t, 2H, $J=6.4$ Hz), 2.37 (m, 2H), 2.29 (m, 2H), 2.24 (s, 6H), 1.50~1.56 (m, 4H). IR (film, cm^{-1}) 3061, 3029, 2943, 2856, 2816, 1600, 1508, 1458, 1248, 1061, 913, 743. MS (ES+) m/e 438 (M+1). Anal. Calcd for $\text{C}_{25}\text{H}_{31}\text{N}_3\text{O}_2\text{S}$: C, 68.62; H, 7.14; N, 9.60; S, 7.33. Found C, 68.56; H, 7.20; N, 9.81; S, 7.24.

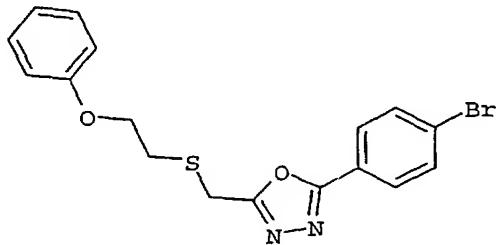
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Example 130

Preparation of 2-{{(2-Phenoxyethyl)thio)methyl}-5-{4-[5-(N,N-dimethylamino)pentyn-1-yl]phenyl}-1,3,4-oxadiazole



20 a) 2-{{(2-Phenoxyethyl)thio)methyl}-5-(4-bromophenyl)-1,3,4-oxadiazole

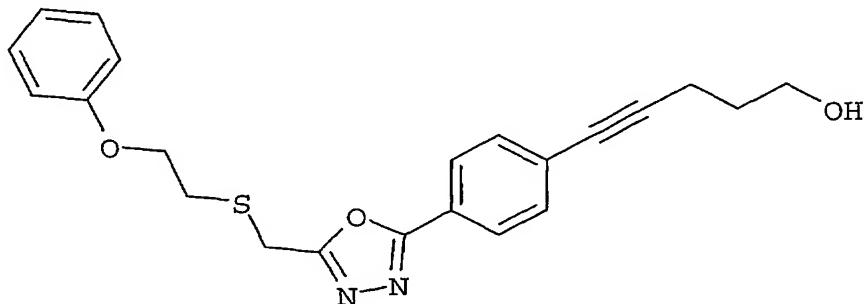


To a mixture of 4-bromobenzoic hydrazide (2.58 g, 12 mmol), 2-{{(2-phenoxyethyl)thio)methyl} acetic acid (2.12 g, 10 mmol), and 4-(N,N-

dimethylamino)phenyldiphenylphosphine (9.16 g, 30 mmol) in acetonitrile (100 mL) at 0 °C was added triethylamine (5.06 g, 50 mmol) in carbon tetrachloride (7.69 g, 50 mmol). After 15 min the cooling bath was removed and the mixture was stirred at room temperature overnight. The mixture was concentrated to approximately half the original 5 volume and partitioned between ether (150 mL) and 2 M HCl (100 mL). The ether layer was washed with 2 M HCl (4 x 30 mL), dried (MgSO_4), and concentrated. The residue was triturated from methylene chloride and hexanes to give white powder (2.80 g, 72%).

10 $^1\text{H NMR}$ (CDCl_3) δ 7.87 (d, 2H, $J=8.8$ Hz), 7.62 (d, 2H, $J=8.8$ Hz), 7.23~7.27 (m, 2H), 6.93 (t, 1H, $J=7.5$ Hz), 6.87 (d, 2H, $J=7.7$ Hz), 4.19 (t, 2H, $J=6.2$ Hz), 4.04 (s, 2H), 3.03 (t, 2H, $J=6.2$ Hz). MS (ES+) m/e 392 (M+1).

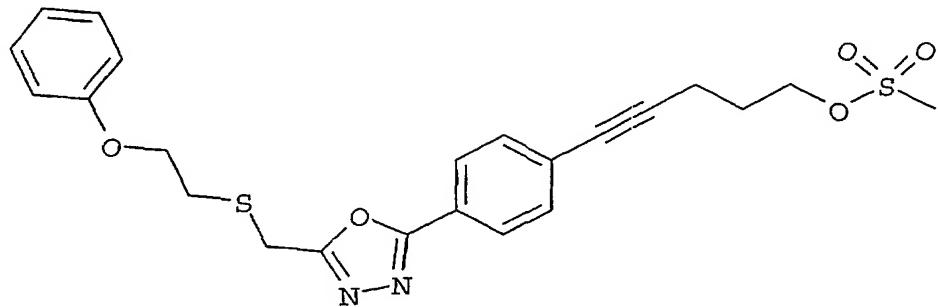
b) 2-{{[(2-Phenoxyethyl)thio]methyl}-5-[4-(5-hydroxypentyn-1-yl)phenyl]-1,3,4-oxadiazole



Palladium (II) acetate (30 mg, 0.13 mmol) and copper (I) iodide (30 mg, 0.16 mmol) were added to a solution of 2-{{[(2-phenoxyethyl)thio]methyl}-5-(4-bromophenyl)-1,3,4-oxadiazole (782 mg, 2 mmol), 4-pentyn-1-ol (186 mg, 2.2 mmol), triphenylphosphine (104 mg, 0.4 mmol), and diethylamine (438 mg, 6 mmol) in dimethylsulfoxide (15 mL). The mixture was stirred at 90 °C for 5 h, diluted with water (20 mL), and extracted with ethyl acetate (3 x 15 mL). The combined ethyl acetate extracts were washed with water (2 x 20 mL) and brine (20 mL), dried (MgSO_4), and concentrated. The residue was purified by column chromatography (silica gel, ethyl acetate/hexanes 1:2) to give a yellow oil (704 mg, 89%).

15 $^1\text{H NMR}$ (CDCl_3) δ 7.92 (d, 2H, $J=8.5$ Hz), 7.47 (d, 2H, $J=8.5$ Hz), 7.22~7.26 (m, 2H), 6.93 (t, 1H, $J=7.3$ Hz), 6.87 (d, 2H, $J=7.7$ Hz), 4.19 (t, 2H, $J=6.0$ Hz), 4.03 (s, 2H), 3.81 (t, 2H, $J=6.2$ Hz), 3.03 (t, 2H, $J=6.0$ Hz), 2.56 (t, 2H, $J=6.9$ Hz), 1.86 (quint, 2H, $J=6.9$ Hz). MS (ES+) m/e 395 (M+1).

c) 2-{{(2-Phenoxyethyl)thio]methyl}-5-{4-[5-(methylsulfonyloxy)pentyn-1-yl]phenyl}-1,3,4-oxadiazole

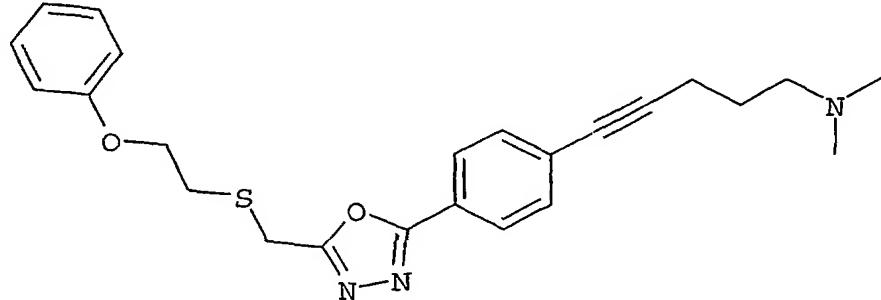


5 To a solution of 2-{{(2-phenoxyethyl)thio]methyl}-5-[4-(5-hydroxypentyn-1-yl)phenyl]-1,3,4-oxadiazole (205 mg, 0.5 mmol) and triethylamine (250 mg, 2.5 mmol) in methylene chloride (5 mL) was added methanesulfonyl chloride (115 mg, 1 mmol). The mixture was stirred at room temperature overnight, diluted with methylene chloride (10 mL), washed with 2 M NaOH (3 x 10 mL), dried (MgSO_4), and concentrated to give a yellow oil (235, 100%).

10 ^1H NMR (CDCl_3) δ 7.93 (d, 2H, $J=8.4$ Hz), 7.48 (d, 2H, $J=8.4$ Hz), 7.23~7.27 (m, 2H), 6.93 (t, 1H, $J=7.3$ Hz), 6.87 (d, 2H, $J=7.7$ Hz), 4.40 (t, 2H, $J=6.1$ Hz), 4.19 (d, 2H, $J=6.0$ Hz), 4.04 (s, 2H), 3.03 (t, 2H, $J=6.0$ Hz), 3.02 (s, 3H), 2.61 (t, 2H, $J=6.8$ Hz), 2.05 (quint, 2H, $J=6.9$ Hz). MS (ES+) m/e 473 (M+1).

15

d) 2-{{(2-Phenoxyethyl)thio]methyl}-5-{4-[5-(N,N-dimethylamino)pentyn-1-yl]phenyl}-1,3,4-oxadiazole



20 A mixture of 2-{{(2-phenoxyethyl)thio]methyl}-5-[4-[5-(methylsulfonyloxy)pentyn-1-yl]phenyl]-1,3,4-oxadiazole (220 mg, 0.5 mmol), 2 M dimethylamine in tetrahydrofuran (1 mL, 2 mmol), and potassium carbonate (690 mg, 5

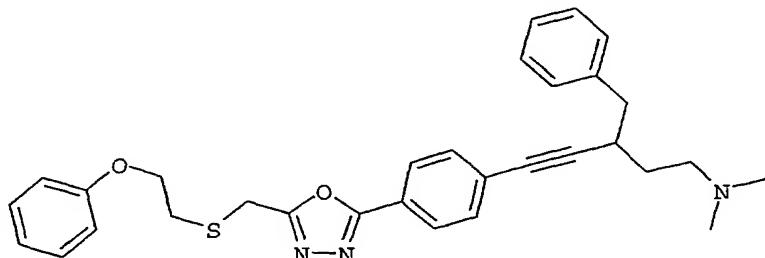
mmol) in acetonitrile (5 mL) was stirred under reflux overnight. The mixture was cooled to room temperature and filtered. The filtrate was concentrated and purified by preparative TLC (silica gel, 10% methanol/methylene chloride) to give a yellow oil (101 mg, 50%).

5 ¹H NMR (CDCl₃) δ 7.92 (d, 2H, J=8.4 Hz), 7.47 (d, 2H, J=8.4 Hz), 7.22~7.26 (m, 2H), 6.93 (t, 1H, J=7.3 Hz), 6.87 (d, 2H, J=8.1 Hz), 4.19 (d, 2H, J=6.2 Hz), 4.03 (s, 2H), 3.03 (t, 2H, J=6.2 Hz), 2.47 (t, 2H, J=7.3 Hz), 2.41 (t, 2H, J=7.3 Hz), 1.81 (s, 6H), 1.77 (quint, 2H, J=7.3 Hz). IR (film, cm⁻¹) 3020, 2997, 2946, 2885, 2212, 1406, 1347, 1225, 1120, 1088. MS (ES+) m/e 422 (M+1). Anal. Calcd for C₂₄H₂₇N₃O₂S: C, 68.38; H, 6.46; 10 N, 9.97; S, 7.61. Found C, 68.26; H, 6.59; N, 9.64; S, 7.69.

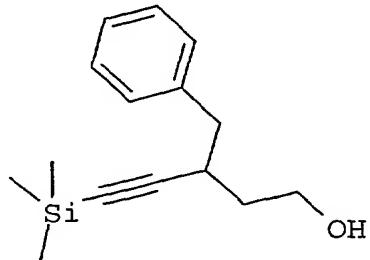
Example 131

Preparation of (+)-2-{{[(2-Phenoxyethyl)thio]methyl}}-5-{4-[3-benzyl-5-(N,N-dimethylamino)pentyn-1-yl]phenyl}-1,3,4-oxadiazole

15



a) (+)-3-Benzyl-5-hydroxy-1-trimethylsilyl-1-pentyne



20

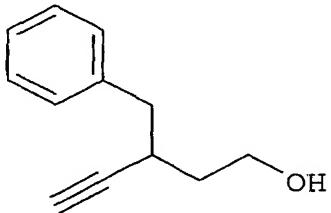
A solution of 5-(trimethylsilyl)-4-pentyn-1-ol (20 g, 128 mmol) and N,N,N',N'-tetramethylethylenediamine (42.5 mL, 282 mmol) in anhydrous THF (650 mL) was

stirred under nitrogen and cooled to -30° C (dry ice/methylene chloride). n-Butyllithium (2.0 M in cyclohexane, 70.5 mL, 141 mmol) and t-butyllithium (1.7 M in pentanes, 82.8 mL, 141 mmol) were sequentially added slowly, while the temperature was maintained

between -25° and -35° C. After complete addition, the mixture was stirred for 2 h, within this temperature range. The mixture was then cooled to -78° C (dry ice/acetone) and benzyl bromide (16 mL, 134 mmol) in tetrahydrofuran (400 mL) was added dropwise while temperature was maintained below -60° C. The reaction was then allowed to warm 5 to room temperature over 3 h. The reaction was quenched with saturated aqueous ammonium chloride (400 mL) and extracted with ethyl ether (2x300 mL). The organic material was dried (Na_2SO_4), filtered and concentrated to yield 35 g of a yellow liquid. This was purified on silica gel (20% ethyl acetate/hexanes) to yield 23.9 g (76%) of a yellow liquid.

10 ^1H NMR (CDCl_3) δ 7.28 (m, 3H), 7.22 (d, 2H, $J=7$ Hz), 3.79 (dd, 2H, $J=5$ and 6 Hz), 2.74-2.85 (m, 3H), 2.36 (t, 1H, $J=14$ Hz), 1.64-1.77 (m, 2H). MS (ES+) m/e 247 ($M+1$).

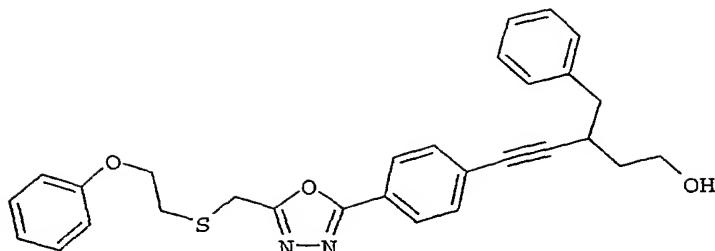
15 b) (+)-3-Benzyl-5-hydroxy-1-pentyne



15 A solution (+)-3-benzyl-5-hydroxy-1-trimethylsilyl-1-pentyne (12.5 g, 50.8 mmol) in methanol (300 mL) saturated with potassium fluoride was refluxed for 1 h. The reaction was cooled to room temperature, diluted with brine (100 mL) and extracted with ethyl ether (3x100 mL). The organic material was washed with brine (2x50 mL), dried (MgSO_4), filtered and concentrated to yield a colorless liquid. This was purified by silica gel (33% ethyl acetate/hexanes) to yield 3.68 g (42%) of a colorless liquid.

20 ^1H NMR (CDCl_3) δ 7.30 (m, 5H), 3.83 (d, 2H, $J=4$ Hz), 2.77-2.88 (m, 3H), 2.12 (s, 1H), 1.78 (m, 1H), 1.66 (m, 1H), 1.53 (br s, 1H). MS (ES+) m/e 175 ($M+1$).

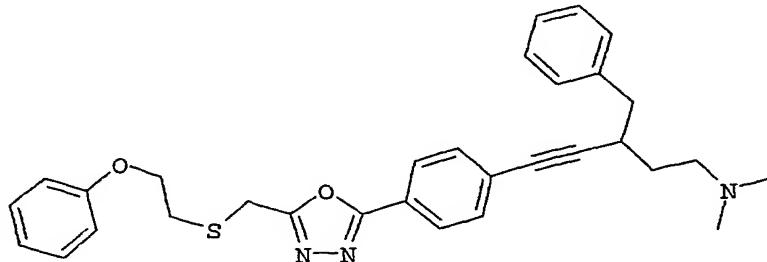
25 c) (+)-2-{[(2-Phenoxyethyl)thio]methyl}-5-[4-(1-(3-benzyl-5-hydroxypentyn-1-yl)phenyl]-1,3,4-oxadiazole



A mixture containing 2-[(2-phenoxyethyl)thio]methyl-5-(4-bromophenyl)-1,3,4-oxadiazole (980 mg, 2.5 mmol), triphenyl-phosphine (131 mg, 0.5 mmol) and palladium (II) acetate (56 mg, 0.25 mmol) was stirred in anhydrous DMSO (10 mL) at room temperature under nitrogen. Solutions of (+)-3-benzyl-5-hydroxy-1-pentyne (480 mg, 2.75 mmol) in methyl sulfoxide (2 mL) and diethylamine (0.78 mL, 7.5 mmol) in methyl sulfoxide (5 mL) were subsequently added, followed by copper (I) iodide (5 mg, 0.025 mmol). This mixture was heated to 90° C for 4h. The reaction was cooled to room temperature, quenched with water (15 mL) and extracted with methylene chloride (3x40 mL). The organic material was washed with water (20 mL), dried (MgSO_4), filtered and concentrated to yield 1.67 g of a brown oil. This oil was purified by silica gel (33% ethyl acetate-hexanes) to yield 856 mg (71%) of a colorless oil.

^1H NMR (CDCl_3) δ 7.94 (d, 2H, $J=9$ Hz), 7.44 (d, 2H, $J=9$ Hz), 7.28 (m, 7H), 6.96 (dd, 1H, $J=8$ and 9 Hz), 6.89 (d, 2H, $J=9$ Hz), 4.21 (t, 2H, $J=12$ Hz), 4.06 (s, 2H), 3.89 (d, 2H, $J=4$ Hz), 3.09 (m, 1H), 3.06 (t, 2H, $J=12$ Hz), 2.92 (m, 2H), 1.90 (m, 1H), 1.78 (m, 1H), 1.52 (br s, 1H). MS (ES+) m/e 485 (M+1).

d) (+)-2-[(2-Phenoxyethyl)thio]methyl-5-[4-(3-benzyl-5-(N,N-dimethylamino)pentyn-1-yl)phenyl]-1,3,4-oxadiazole



20

A solution of (+)-2-[(2-Phenoxyethyl)thio]methyl-5-[4-(3-benzyl-5-hydroxypentyn-1-yl)phenyl]-1,3,4-oxadiazole (250 mg, 0.52 mmol), triethylamine (0.36 mL, 2.58 mmol) and methanesulfonyl chloride (0.08 mL, 1.04 mmol) were stirred in

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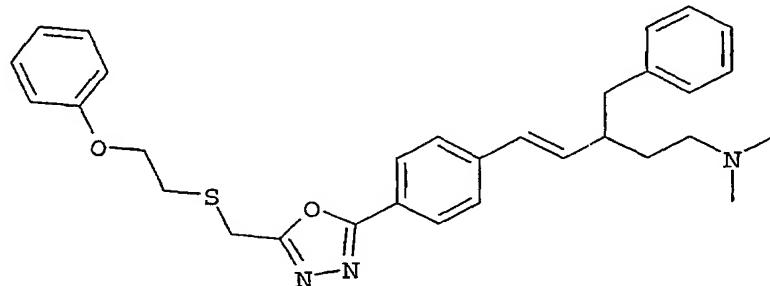
methylene chloride (5 mL) at room temperature for 16 h. The mixture was diluted with methylene chloride (20 mL), extracted with 2N NaOH (20 mL), dried (MgSO_4), filtered and concentrated to yield a quantitative amount of the corresponding mesylate.

The mesylate was combined with dimethylamine (2.0 M in THF, 1.03 mL, 2.06 mmol) and potassium carbonate (720 mg, 5.2 mmol) in acetonitrile (10 mL) and refluxed for 6 h. Since the reaction was not complete after 6 h., it was allowed to react at room temperature for an additional 16 h. After filtering the solids, the filtrate was concentrated to yield 231 mg of a brown oil. This was purified by preparative TLC (10% methanol/methylene chloride) to yield 73 mg (27%) of a colorless oil.

10 ^1H NMR (CDCl_3) δ 7.91 (d, 2H, $J=8$ Hz), 7.41 (d, 2H, $J=8$ Hz), 7.26 (m, 7H), 6.93 (dd, 1H, $J=7$ and 8 Hz), 6.87 (d, 2H, $J=9$ Hz), 4.19 (t, 2H, $J=12$ Hz), 4.03 (s, 2H), 3.03 (t, 2H, $J=12$ Hz), 2.93 (m, 1H), 2.85 (m, 2H), 2.47 (m, 2H), 2.21 (s, 6H), 1.74 (m, 1H), 1.65 (m, 1H). MS (ES+) m/e 512 (M+1). IR (film, cm^{-1}) 3410, 2936, 1601, 1493, 1462, 1239, 752, 698. Anal. Calcd for $\text{C}_{31}\text{H}_{33}\text{N}_3\text{O}_2\text{S}$: C, 72.77; H, 6.50; N, 8.21; S, 6.27. Found C, 15 72.45; H, 6.33; N, 8.16; S, 6.18.

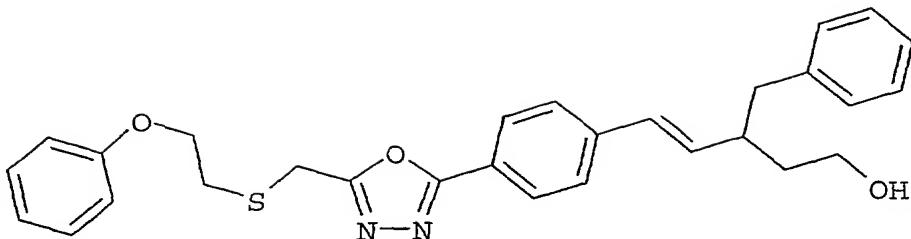
Example 132

Preparation of (E)-(+)-2-{{[(2-phenoxyethyl)thio]methyl}-5-[4-[3-benzyl-5-(N,N-dimethylamino)penten-1-yl]phenyl]-1,3,4-oxadiazole



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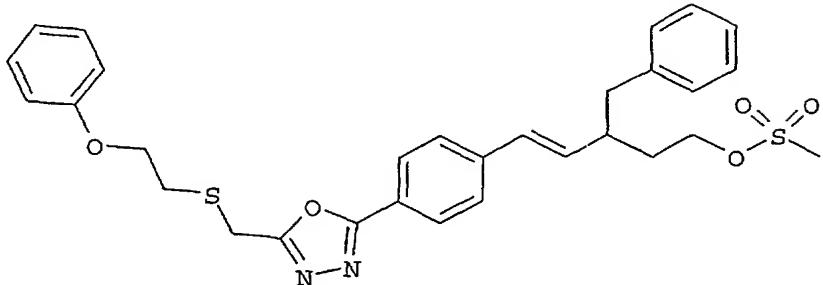
a) (E)-(+)-2-{{[(2-phenoxyethyl)thio]methyl}-5-[4-(3-benzyl-5-hydroxypenten-1-yl)phenyl]-1,3,4-oxadiazole



A solution containing Red-Al (65 wt% in toluene, 0.2 mL, 0.67 mmol) in anhydrous tetrahydrofuran (5.5 mL) was stirred in an ice-water bath under nitrogen. A solution of (+)-2-{{[(2-phenoxyethyl)thio]methyl}-5-[4-(1-(3-benzyl-5-hydroxypentyn-1-yl)phenyl]-1,3,4-oxadiazole (0.27 g, 0.56 mmol) in anhydrous tetrahydrofuran (10 mL) was added and stirring was continued in the cooling bath until the bubbling due to hydrogen evolution had ceased. The bath was then removed and the reaction was refluxed for 2 h. Since the reaction had not completed, the mixture was again cooled in an ice-water bath and more Red-Al (0.1 mL, 0.33 mmol) was added. The reaction was 5 refluxed for another 1.5 h until starting material was gone. The mixture was then cooled in an ice-water bath and quenched with water (3 mL). The mixture was then extracted with ethyl acetate (2x10 mL). The combined organic material was extracted with brine (2x10 mL), dried (MgSO_4), filtered and concentrated to yield 257 mg of a yellow oil. 10 This material was purified by chromatography (50% ethyl acetate/hexanes) to yield 34 mg 15 (12%) of a white solid. This procedure was repeated twice to generate enough material to continue.

^1H NMR (CDCl_3) δ 7.92 (d, 2H, $J=9$ Hz), 7.38 (d, 2H, $J=9$ Hz), 7.25 (m, 4H), 7.16 (m, 3H), 6.93 (dd, 1H, $J=7$ and 7 Hz), 6.87 (d, 2H, $J=8$ Hz), 6.32 (d, 1H, $J=6$ Hz), 6.16 (dd, 1H, $J=6$ and 9 Hz), 4.18 (t, 2H, $J=12$ Hz), 4.03 (s, 2H), 3.68 (m, 2H), 3.03 (t, 2H, $J=12$ Hz), 2.75 (d, 2H, $J=7$ Hz), 2.52 (m, 1H), 1.81 (m, 1H), 1.63 (m, 1H), 1.20 (m, 1H). 20 MS (ES+) m/e 487 (M+1).

- b) (+)-2-{[(2-Phenoxyethyl)thio]methyl}-5-{4-[3-benzyl-5-(methylsulfonyloxy)penten-1-yl]phenyl}-1,3,4-oxadiazole

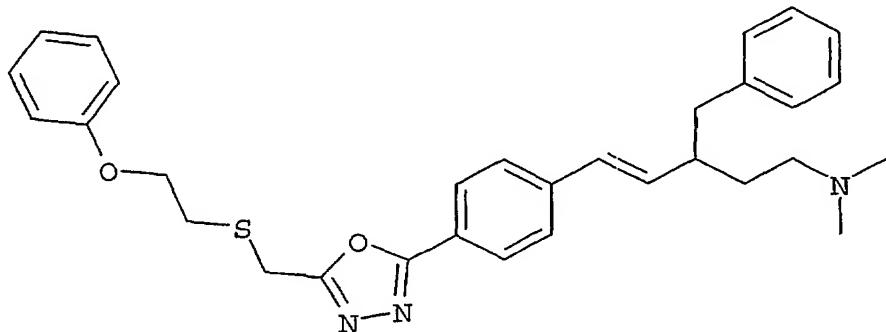


To a solution of (E)-(+)-2-{[(2-phenoxyethyl)thio]methyl}-5-[4-(3-benzyl-5-hydroxypenten-1-yl)phenyl]-1,3,4-oxadiazole (60 mg, 0.12 mmol) and triethylamine (50 mg, 0.5 mmol) in methylene chloride (2 mL) at 0 °C was added methanesulfonyl chloride (29 mg, 0.25 mmol). The resultant mixture was stirred at room temperature overnight, diluted with methylene chloride (20 mL), washed with 2 M HCl (5 mL) and 2 M NaOH (5 mL), dried (MgSO_4), and concentrated to give a yellow oil (61 mg, 90%).

¹⁰ ^1H NMR (CDCl_3) δ 7.93 (d, 2H, $J=8.6$ Hz), 7.38 (d, 2H, $J=8.6$ Hz), 7.20~7.31 (m, 4H), 7.18 (t, 1H, $J=7.0$ Hz), 7.14 (d, 2H, $J=7.0$ Hz), 6.93 (t, 1H, $J=7.8$ Hz), 6.87 (d, 2H, $J=7.8$ Hz), 6.35 (d, 1H, $J=15.6$ Hz), 6.10 (dd, 1H, $J=15.6, 8.9$ Hz), 4.20~4.26 (m, 2H), 4.19 (d, 2H, $J=6.2$ Hz), 4.03 (s, 2H), 3.03 (t, 2H, $J=6.2$ Hz), 2.91 (s, 3H), 2.76 (d, 2H, $J=6.3$ Hz), 2.03 (m, 1H), 1.75 (m, 1H), 1.38 (m, 1H). MS (ES+) m/e 565 (M+1).

¹⁵

- c) (+)-2-{[(2-Phenoxyethyl)thio]methyl}-5-{4-[3-benzyl-5-(N,N-dimethylamino)penten-1-yl]phenyl}-1,3,4-oxadiazole



A mixture of (+)-2-{[(2-phenoxyethyl)thio]methyl}-5-{4-[3-benzyl-5-(methylsulfonyloxy)penten-1-yl]phenyl}-1,3,4-oxadiazole (61 mg, 0.11 mmol), 2 M ²⁰ dimethylamine in tetrahydrofuran (0.6 mL, 1.2 mmol), and potassium carbonate (166 mg,

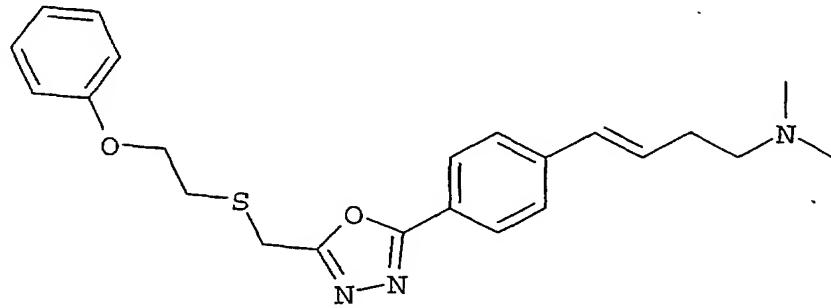
-273-

1.2 mmol) in acetonitrile (10 mL) was stirred under reflux for 20 h and filtered. The filtrate was concentrated and purified by preparative TLC (silica gel, 10% methanol/methylene chloride) to give a white solid (32 mg, 57%).

¹H NMR (CDCl₃) δ 7.92 (d, 2H, J=8.6 Hz), 7.38 (d, 2H, J=8.6 Hz), 7.13~7.26 (m, 5 H), 6.93 (t, 1H, J=7.8 Hz), 6.87 (d, 2H, J=7.8 Hz), 6.28 (d, 1H, J=16.4 Hz), 6.13 (dd, 1H, J=16.3, 8.5 Hz), 4.18 (t, 2H, J=6.2 Hz), 4.03 (s, 2H), 3.03 (t, 2H, J=6.2 Hz), 2.74 (d, 2H, J=7.0 Hz), 2.55 (m, 1H), 2.32 (t, 2H, J=7.8 Hz), 2.21 (s, 6H), 1.74 (m, 1H), 1.55 (m, 1H). IR (KBr, cm⁻¹) 3032, 2955, 2906, 1600, 1557, 1476, 1348, 1179, 1126, 747. MS (ES+) m/e 514 (M+1). Anal. Calcd for C₃₁H₃₅N₃O₂S: C, 72.48; H, 6.87; N, 8.18; S, 6.24. 10 Found C, 71.91; H, 6.81; N, 8.23; S, 6.34.

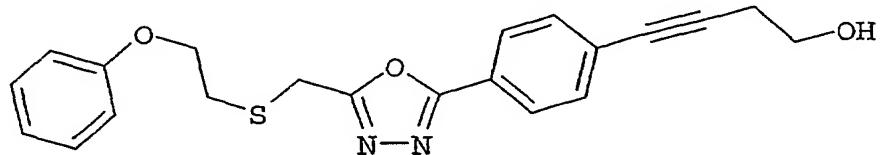
Example 133

Preparation of 2-{{(2-Phenoxyethyl)thio}methyl}-5-{4-[4-(N,N-dimethylamino)buten-1-yl]phenyl}-1,3,4-oxadiazole



15

a) 2-{{(2-phenoxyethyl)thio}methyl}-5-[4-(4-hydroxybutyn-1-yl)phenyl]-1,3,4-oxadiazole



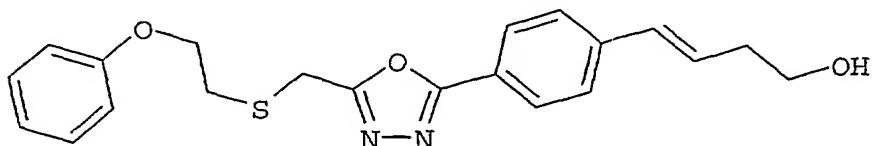
A mixture containing 2-{{(2-phenoxyethyl)thio}methyl}-5-(4-bromophenyl)-1,3,4-oxadiazole (5g, 12.8 mmol), triphenyl-phosphine (0.67 g, 2.56 mmol) and palladium (II) acetate (287 mg, 1.28 mmol) was stirred in anhydrous dimethylsulfoxide (50 mL) at room temperature under nitrogen. Solutions of 3-butyn-1-ol (1.07 mL, 14.1 mmol) in dimethylsulfoxide (10 mL) and diethylamine (4 mL, 38.4 mmol) in dimethylsulfoxide (10 mL) were subsequently added, followed by copper (I) iodide (25 mg, 0.128 mmol). This

mixture was heated to 90° C for 3 h. The reaction was cooled to room temperature, quenched with water (75 mL) and extracted with ethyl acetate (3x100 mL). The organic material was washed with brine (3x50 mL), dried (MgSO_4), filtered and concentrated to yield 5.92 g of a brown oil. This oil was purified by silica gel (50% ethyl acetate/hexanes) to yield 1.91 g (39%) of a colorless oil.

¹H NMR (CDCl_3) δ 7.94 (d, 2H, $J=8$ Hz), 7.50 (d, 2H, $J=8$ Hz), 7.28 (m, 2H), 6.93 (dd, 1H, $J=7$ and 8 Hz), 6.87 (d, 2H, $J=8$ Hz), 4.19 (t, 2H, $J=12$ Hz), 4.03 (s, 2H), 3.83 (dd, 2H, $J=6$ and 12 Hz), 3.09 (m, 1H), 3.04 (t, 2H, $J=12$ Hz), 2.71 (t, 2H, $J=12$ Hz), 1.76 (t, 1H, $J=12$ Hz). MS (ES+) m/e 381 (M+1).

10

b) (E)-2-{[(2-phenoxyethyl)thio]methyl}-5-[4-(4-hydroxybuten-1-yl)phenyl]-1,3,4-oxadiazole

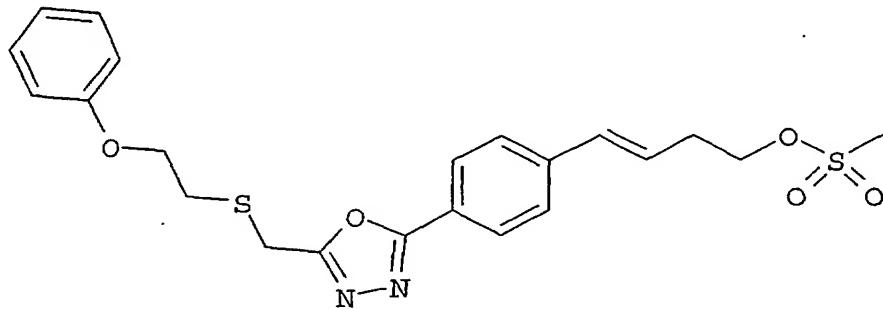


A solution containing Red-Al (0.73 mL, 2.4 mmol) in anhydrous tetrahydrofuran (12 mL) was stirred in an ice-water bath under nitrogen. A solution of 2-{[(2-phenoxyethyl)thio]methyl}-5-[4-(4-hydroxybutyn-1-yl)phenyl]-1,3,4-oxadiazole (0.76 g, 2.0 mmol) in anhydrous tetrahydrofuran (10 mL) was added and stirring was continued in the cooling bath until the bubbling due to hydrogen evolution had ceased. The bath was then removed and the reaction was refluxed for 1 h. Even though some of the alkyne starting material was present, the reaction was stopped here because TLC indicated that the product was decomposing. The mixture was then cooled in an ice-water bath and quenched with water (5 mL). The mixture was diluted with more water (10 mL) and then extracted with ethyl acetate (3x30 mL). The combined organic material was extracted with brine (2x20 mL), dried (MgSO_4), filtered and concentrated to yield 890 mg of a yellow oil which contained products and the alkyne starting material. This material was purified by preparative TLC (50% ethyl acetate/hexanes) to yield 128 mg (22%, based on converted starting material) of a white solid and 187 mg of alkyne starting material.

¹H NMR (CDCl_3) δ 7.94 (d, 2H, $J=8$ Hz), 7.45 (d, 2H, $J=8$ Hz), 7.25 (m, 4H), 7.25 (m, 2H), 6.94 (dd, 1H, $J=7$ and 8 Hz), 6.87 (d, 2H, $J=8$ Hz), 6.52 (d, 1H, $J=15$ Hz), 6.36

(m, 1H), 4.18 (t, 2H, J=12 Hz), 4.03 (s, 2H), 3.78 (m, 2H), 3.03 (t, 2H, J=12 Hz), 2.75 (d, 2H, J=7 Hz), 2.52 (m, 2H), 1.43 (m, 1H). MS (ES+) m/e 383 (M+1).

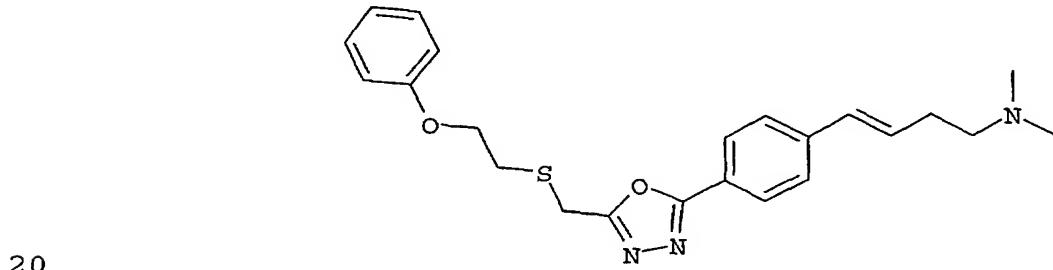
- 5 c) (E)-2-{{(2-Phenoxyethyl)thio}methyl}-5-{4-[4-(methylsulfonyloxy)buten-1-yl]phenyl}-1,3,4-oxadiazole



To a solution of (E)-2-{{(2-phenoxyethyl)thio}methyl}-5-[4-(4-hydroxybuten-1-yl)phenyl]-1,3,4-oxadiazole (120 mg, 0.31 mmol) and triethylamine (121 mg, 1.2 mmol) in methylene chloride (3 mL) at 0 °C was added methanesulfonyl chloride (69 mg, 0.6 mmol). The resultant mixture was stirred at room temperature overnight, diluted with methylene chloride (20 mL), washed with 2 M HCl (5 mL) and 2 M NaOH (5 mL), dried (MgSO₄), and concentrated to give yellow oil (138 mg, 97%).

10 ¹H NMR (CDCl₃) δ 7.95 (d, 2H, J=8.6 Hz), 7.44 (d, 2H, J=8.6 Hz), 7.22~7.27 (m, 2H), 6.93 (t, 1H, J=7.8 Hz), 6.87 (d, 2H, J=7.8 Hz), 6.54 (d, 1H, J=16.4 Hz), 6.28 (dt, 1H, J=16.4, 7.0 Hz), 4.34 (t, 2H, J=6.2 Hz), 4.19 (t, 2H, J=6.2 Hz), 4.03 (s, 2H), 3.04 (t, 2H, J=6.2 Hz), 3.01 (s, 3H), 2.68 (m, 2H). MS (ES+) m/e 461 (M+1).

- d) (E)-2-{{(2-Phenoxyethyl)thio}methyl}-5-{4-[4-(N,N-dimethylamino)buten-1-yl]phenyl}-1,3,4-oxadiazole



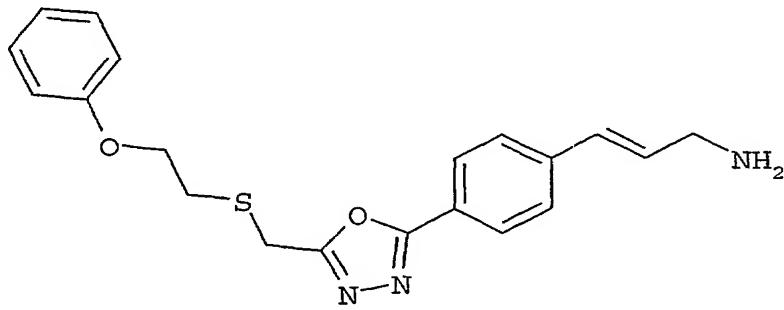
20 A mixture of (E)-2-{{(2-Phenoxyethyl)thio}methyl}-5-{4-[4-(methylsulfonyloxy)buten-1-yl]phenyl}-1,3,4-oxadiazole (120 mg, 0.29 mmol), 2 M

dimethylamine in tetrahydrofuran (1.5 mL, 3 mmol), and potassium carbonate (400 mg, 2.9 mmol) in acetonitrile (15 mL) was stirred under reflux for 20 h and filtered. The filtrate was concentrated and purified by preparative TLC (silica gel, 10% methanol/methylene chloride) to give a white solid (111 mg, 93%).

- 5 ^1H NMR (CDCl_3) δ 7.92 (d, 2H, $J=7.8$ Hz), 7.43 (d, 2H, $J=8.6$ Hz), 7.22~7.27 (m, 2H), 6.93 (t, 1H, $J=7.4$ Hz), 6.87 (d, 2H, $J=7.6$ Hz), 6.46 (d, 1H, $J=15.6$ Hz), 6.35 (dt, 1H, $J=15.6, 6.2$ Hz), 4.19 (t, 2H, $J=6.2$ Hz), 4.03 (s, 2H), 3.03 (t, 2H, $J=6.2$ Hz), 2.40-2.49 (m, 4H), 2.28 (s, 6H). IR (KBr, cm^{-1}) 3032, 2960, 2931, 2880, 1589, 1553, 1499, 1239, 1094, 1042, 746. MS (ES+) m/e 410 (M+1). Anal. Calcd for $\text{C}_{23}\text{H}_{27}\text{N}_3\text{O}_2\text{S}$: C, 67.45; H, 6.65; N, 10.26; S, 7.83. Found C, 67.32; H, 6.68; N, 10.50; S, 7.88.
- 10

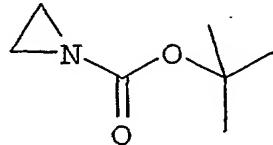
Example 134

Preparation of (E)-2-{{[(2-Phenoxyethyl)thio]methyl}-5-[4-(3-aminopropen-1-yl)phenyl]-1,3,4-oxadiazole



15

- a) 1-tert-Butoxycarbonylaziridine.

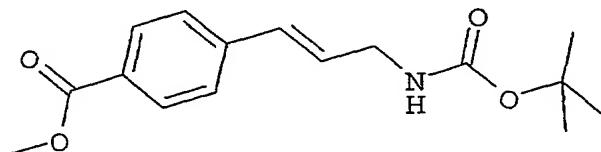


A solution containing ethanolamine (6 g, 98.2 mmol) and di-tert-butyl dicarbonate (23.6 g, 108 mmol) in isopropyl alcohol (40 mL) and dioxane (80 mL) was stirred at room temperature for 3 hr. The mixture was concentrated and dried under vacuum overnight. This material was then combined with p-toluenesulfonyl chloride (22.5 g, 117.8 mmol) and powdered KOH (22.0 g, 392.8 mmol) in ethyl ether (800 mL). The mixture was refluxed for 1.5 days, but only 50% was converted. More KOH (11 g, 146 mmol) was added, the heat was removed and the reaction stirred 2 days at room temperature. The

mixture was poured over ice-water (600 mL) and the organic material was separated. The aqueous layer was extracted with ethyl ether (200 mL) and the combined organic extracts were dried (MgSO_4), filtered and concentrated at 1 atm to remove most of the ether. The flask was left open in the hood overnight to allow complete evaporation of ether to yield
 5 14 g (99%) of a colorless oil.

^1H NMR (CDCl_3) δ 2.11 (s, 4H), 1.43 (s, 9H).

b) Methyl 4-{3-[(tert-butoxycarbonyl)amino]propen-1-yl}benzoate

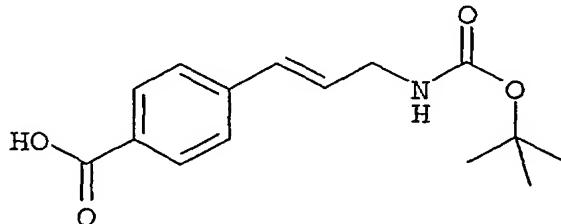


A solution containing methyl 4-formylbenzoate (2.7 g, 16.45 mmol), 1-(tert-butoxycarbonyl)aziridine (7.07 g, 49.4 mmol), and triphenylphosphine (12.9 g, 49.4 mmol) in isopropyl alcohol (150 mL) was refluxed for 3h. The reaction was concentrated to yield 4.63 g of a colorless oil which contained an approximately 1:3 ratio of Z-olefin (top spot on TLC) to E-olefin (bottom spot). This material was purified on silica gel (20% ethyl acetate/hexanes) to yield 1.24 g (26%) of a white solid (E-isomer). Another 15 2.2 g (46%) of E/Z mixture was isolated, too.

E-isomer: ^1H NMR (CDCl_3) δ 7.95 (d, 2H, $J=8$ Hz), 7.38 (d, 2H, $J=8$ Hz), 6.51 (d, 1H, $J=16$ Hz), 6.29 (m, 1H), 4.68 (br s, 1H), 3.91 (m, 2H), 3.88 (s, 3H), 1.44 (s, 9H). MS (ES+) m/e 292 ($M+1$).

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c) 4-{3-[(tert-butoxycarbonyl)amino]propen-1-yl}benzoic acid, (E)- and (Z)-isomers



To a solution of methyl 4-{3-[(tert-butoxycarbonyl)amino]propen-1-yl}benzoate (1.46 g, 5 mmol) in 1,4-dioxane (25 mL) was added 2 M NaOH (25 mL, 50 mmol) and
 25 the reaction was stirred at room temperature for 3 h. Ice (30 g) was added and the mixture

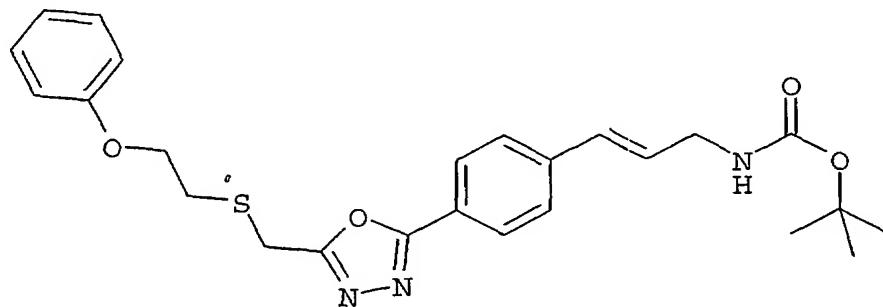
was acidified with 2 M HCl (26 mL) and extracted with methylene chloride (3 x 30 mL). The combined methylene chloride extracts were washed with water (2 x 50 mL), dried (MgSO₄), and concentrated to give a white solid (1.20 g, 86%).

E-isomer: ¹H NMR (CDCl₃) δ 7.96 (d, 2H, J=8.6 Hz), 7.52 (d, 2H, J=8.8 Hz), 6.59 (d, 1H, J=15.6 Hz), 6.43 (dt, 1H, J=15.6, 5.5 Hz), 6.19 (br s, 1H), 3.87 (m, 2H), 1.41 (s, 9H). MS (ES-) m/e 276 (M-1).

Z-isomer: ¹H NMR (CDCl₃) δ 8.04 (d, 2H, J=7.8 Hz), 7.29 (d, 2H, J=8.6 Hz), 6.55 (d, 1H, J=11.7 Hz), 5.77 (dt, 1H, J=11.7, 6.0 Hz), 4.64 (br s, 1H), 4.03 (m, 2H), 1.43 (s, 9H). MS (ES-) m/e 276 (M-1).

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d) 2-{{(2-Phenoxyethyl)thio}methyl}-5-{4-[3-((tert-butoxycarbonyl)amino)propen-1-yl]phenyl}-1,3,4-oxadiazole, (E)- and (Z)-isomers



To a stirred mixture of 4-{3-[(tert-butoxycarbonyl)amino]propen-1-yl}benzoic acid (1.11 g, 4mmol), 2-(2-phenoxyethyl)thioacetic hydrazide hydrochloride (1.16 g, 4.4 mmol), and *p*-(N,N-dimethylamino)phenyldiphenylphosphine (3.66 g, 12 mmol) in acetonitrile (40 mL) at 0 °C was added a solution of triethylamine (2.43 g, 24 mmol) in carbon tetrachloride (3.08 g, 20 mmol). After 10 min the cooling bath was removed and stirring was continued at room temperature overnight. The mixture was concentrated to approximately half the original volume and partitioned between ether (100 mL) and 2 M HCl (100 mL). The ether layer was washed with 2 M HCl (4 x 50 mL) and water (50 mL), dried (MgSO₄) and concentrated. The residue was purified by column chromatography (silica gel, ethyl acetate/hexanes 1:2) to give a colorless oil (1.23 g, 66%).

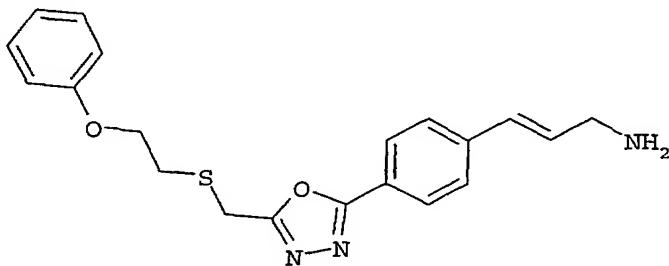
E-isomer: ¹H NMR (CDCl₃) δ 7.95 (d, 2H, J=8.6 Hz), 7.44 (d, 2H, J=7.9 Hz), 7.22~7.26 (m, 2H), 6.92 (t, 1H, J=7.8 Hz), 6.87 (d, 2H, J=7.8 Hz), 6.52 (d, 1H, J=16.4

Hz), 6.31 (dt, 1H, J=16.6, 6.3 Hz), 4.67 (br s, 1H), 4.19 (t, 2H, J=6.2 Hz), 4.03 (s, 2H), 3.93 (m, 2H), 3.03 (t, 2H, J=6.2 Hz), 1.45 (s, 9H). MS (ES+) m/e 468 (M+1).

Z-isomer: ^1H NMR (CDCl_3) δ 7.98 (d, 2H, J=8.6 Hz), 7.32 (d, 2H, J=8.5 Hz), 7.23~7.27 (m, 2H), 6.93 (t, 1H, J=7.8 Hz), 6.86 (d, 2H, J=7.8 Hz), 6.54 (d, 1H, J=11.7 Hz), 5.76 (dt, 1H, J=11.7, 6.3 Hz), 4.62 (br s, 1H), 4.18 (t, 2H, J=6.2 Hz), 4.06 (m, 2H), 4.04 (s, 2H), 3.04 (t, 2H, J=6.2 Hz), 1.43 (s, 9H). MS (ES+) m/e 468 (M+1).

e) 2-{{(2-Phenoxyethyl)thio}methyl}-5-[4-(3-aminopropen-1-yl)phenyl]-1,3,4-oxadiazole, (E)- and (Z)-isomers

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Trifluoroacetic acid (2 mL) was added slowly to a solution of 2-{{(2-phenoxyethyl)thio}methyl}-5-[4-[3-((tert-butoxycarbonyl)amino)propen-1-yl]phenyl]-1,3,4-oxadiazole (467 mg, 1 mmol) in methylene chloride (8 mL). The mixture was stirred at room temperature for 1 h and concentrated. The residue was partitioned between 2 M NaOH (10 mL) and methylene chloride (20 mL), and the aqueous layer was extracted with methylene chloride (15 mL). The combined methylene chloride extracts were dried (MgSO_4) and concentrated. The residue was triturated from methylene and hexanes to give a white powder (323 mg, 88%).

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E-isomer: ^1H NMR (CDCl_3) δ 7.95 (d, 2H, J=8.6 Hz), 7.46 (d, 2H, J=8.6 Hz), 7.23~7.26 (m, 2H), 6.93 (t, 1H, J=7.1 Hz), 6.87 (d, 2H, J=7.8 Hz), 6.54 (d, 1H, J=16.3 Hz), 6.44 (dt, 1H, J=15.6, 5.5 Hz), 4.19 (t, 2H, J=6.2 Hz), 4.03 (s, 2H), 3.51 (d, 2H, J=5.5 Hz), 3.04 (t, 2H, J=6.2 Hz). IR (KBr, cm^{-1}) 3430, 3029, 2952, 2945, 2858, 1600, 1563, 1504, 1461, 1244, 1175, 752. MS (ES+) m/e 368 (M+1). Anal. Calcd for $\text{C}_{20}\text{H}_{21}\text{N}_3\text{O}_2\text{S}$: C, 65.37; H, 5.76; N, 11.43; S, 8.73. Found C, 65.58; H, 6.01; N, 11.20; S, 8.61.

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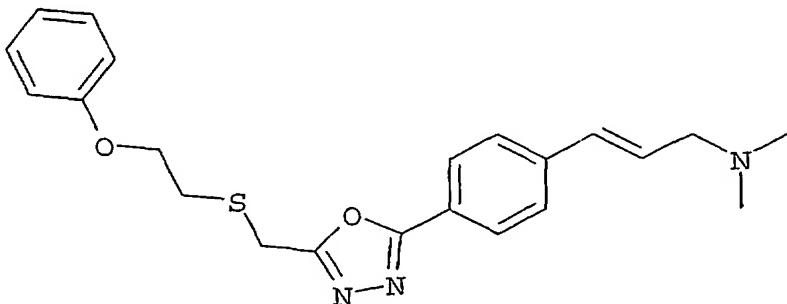
Z-isomer: ^1H NMR (CDCl_3) δ 7.97 (d, 2H, J=8.6 Hz), 7.32 (d, 2H, J=8.7 Hz), 7.22~7.27 (m, 2H), 6.93 (t, 1H, J=7.8 Hz), 6.87 (d, 2H, J=7.8 Hz), 6.47 (d, 1H, J=11.7 Hz), 5.84 (dt, 1H, J=11.7, 5.8 Hz), 4.19 (t, 2H, J=6.2 Hz), 4.04 (s, 2H), 3.60 (d, 2H, J=6.2

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Hz), 3.04 (t, 2H, J=6.3 Hz). IR (KBr, cm⁻¹) 3430, 3031, 2950, 2945, 2841, 1599, 1550, 1486, 1410, 1235, 1147, 755. MS (ES+) m/e 368 (M+1). Anal. Calcd for C₂₀H₂₁N₃O₂S: C, 65.37; H, 5.76; N, 11.43; S, 8.73. Found C, 64.97; H, 5.94; N, 11.26; S, 8.83.

Example 135

- 5 Preparation of 2-{{(2-Phenoxyethyl)thio}methyl}-5-{4-[3-(N,N-dimethylamino)propen-1-yl]phenyl}-1,3,4-oxadiazole, (E)- and (Z)-isomers



A mixture of 2-{{(2-Phenoxyethyl)thio}methyl}-5-{4-(3-aminopropen-1-yl)phenyl}-1,3,4-oxadiazole (229 mg, 0.62 mmol) and paraformaldehyde (187 mg, 6.2 mmol) in methanol (6 mL) was stirred under reflux for 3 h and then cooled to room temperature. Sodium cyanoborohydride (117 mg, 1.86 mmol) was added in three portions and the resultant mixture was stirred at room temperature for 2 h. The reaction was quenched by addition of water (0.5 mL) and most of the methanol was evaporated. The residue was diluted with saturated sodium bicarbonate (10 mL) and extracted with 10 15 methylene chloride (3 x 10 mL). The combined methylene chloride extracts were dried (MgSO₄) and concentrated. The residue was purified by preparative TLC (silica gel, 10% methanol/methylene chloride) to give a pale yellow solid (176 mg, 72%).

E-isomer: ¹H NMR (CDCl₃) δ 7.95 (d, 2H, J=8.6 Hz), 7.46 (d, 2H, J=8.6 Hz), 7.22~7.27 (m, 2H), 6.93 (t, 1H, J=7.8 Hz), 6.87 (d, 2H, J=7.8 Hz), 6.54 (d, 1H, J=15.6 Hz), 6.38 (dt, 1H, J=16.4, 6.3 Hz), 4.19 (t, 2H, J=6.2 Hz), 4.03 (s, 2H), 3.11 (d, 2H, J=6.3 Hz), 3.04 (t, 2H, J=6.2 Hz), 2.28 (s, 6H). IR (film, cm⁻¹) 3030, 2952, 2928, 2884, 1598, 1552, 1481, 1293, 1065, 739. MS (ES+) m/e 396 (M+1). Anal. Calcd for C₂₂H₂₅N₃O₂S: C, 66.81; H, 6.37; N, 10.62; S, 8.11. Found C, 67.05; H, 6.28; N, 10.79; S, 8.04.

Z-isomer: ¹H NMR (CDCl₃) δ 7.98 (d, 2H, J=7.8 Hz), 7.35 (d, 2H, J=7.8 Hz), 7.23~7.27 (m, 2H), 6.93 (t, 1H, J=7.4 Hz), 6.87 (d, 2H, J=7.8 Hz), 6.58 (d, 1H, J=11.7 Hz), 5.90 (dt, 1H, J=12.5, 6.2 Hz), 4.18 (t, 2H, J=6.2 Hz), 4.04 (s, 2H), 3.20 (d, 2H, J=6.2

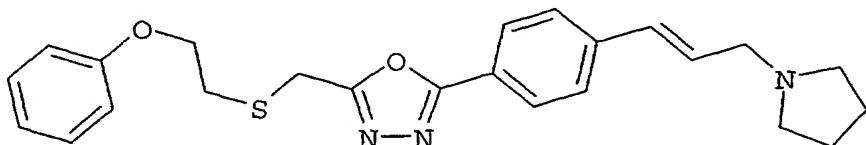
-281-

Hz), 3.04 (t, 2H, J=6.2 Hz), 2.25 (s, 6H). IR (film, cm^{-1}) 3031, 2980, 2963, 1600, 1552, 1481, 1295, 1055, 983, 750. MS (ES+) m/e 396 (M+1). Anal. Calcd for $\text{C}_{22}\text{H}_{25}\text{N}_3\text{O}_2\text{S}$: C, 66.81; H, 6.37; N, 10.62; S, 8.11. Found C, 67.37; H, 6.50; N, 10.43; S, 8.03.

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Example 136

Preparation of (E)-2-{{(2-phenoxyethyl)thio)methyl}-5-[4-(3-pyrrolidinopropen-1-yl)phenyl]-1,3,4-oxadiazole

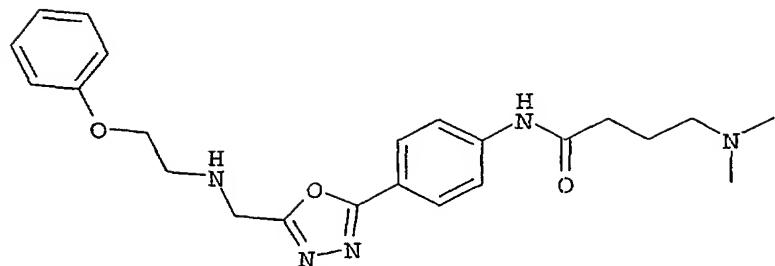


A suspension containing (E)-2-{{(2-phenoxyethyl)thio)methyl}-5-[4-(3-aminopropen-1-yl)phenyl]-1,3,4-oxadiazole (135 mg, 0.367 mmol) and 1,4-butanediol bisulfite adduct (121 mg, 0.367 mmol) was stirred in methanol (4 mL). Sodium cyanoborohydride (46.1 mg, 0.734 mmol) was added and the reaction stirred for 72 h. The reaction was quenched with 2N aqueous NaOH (2 mL), extracted with methylene chloride (3x5 mL), dried (MgSO_4) and filtered to yield 147 mg of a yellow oil. This material was purified by preparative TLC (10% methanol/methylene chloride) to yield 55 mg (36%) of a yellow solid.

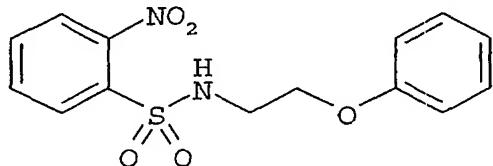
^1H NMR (CDCl_3) δ 7.95 (d, 2H, J=8 Hz), 7.46 (d, 2H, J=8 Hz), 7.24 (m, 2H), 6.93 (dd, 1H, J=7 and 8 Hz), 6.87 (d, 2H, J=8 Hz), 6.57 (d, 1H, J=16 Hz), 6.45 (dd, 1H, J=7 and 16 Hz), 4.18 (t, 2H, J=12 Hz), 4.03 (s, 2H), 3.31 (d, 2H, J=6 Hz), 3.03 (t, 2H, J=12 Hz), 2.60 (m, 4H), 1.81 (m, 4H). IR (film, cm^{-1}) 3428, 2952, 2930, 2787, 1596, 1493, 1241, 755. MS (ES+) m/e 422 (M+1). Anal. Calcd for $\text{C}_{24}\text{H}_{27}\text{N}_3\text{O}_2\text{S}$: C, 68.38; H, 6.46; N, 9.97; S, 7.61. Found C, 68.52; H, 6.38; N, 9.89; S, 7.70.

25 Example 137
Preparation of 2-{{(2-phenoxyethyl)amino)methyl}-5-{4-[(4-(N,N-dimethylamino)butanoyl)amino]phenyl}-1,3,4-oxadiazole

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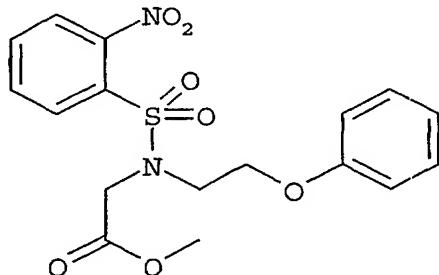
a) 2-(2-Nitrobenzensulfonamido)ethyl phenyl ether



To a stirred mixture of 2-phenoxyethylamine (3.29 g, 24 mmol) and potassium bicarbonate (10 g, 100 mmol) in methylene chloride (200 mL) was added 2-nitrobenzenesulfonyl chloride (4.43 g, 20 mmol) in several portions. The resultant mixture was stirred at room temperature overnight and filtered. The filtrate was washed with 2 M HCl (3 x 30 mL), dried (MgSO₄), and concentrated. The residue was triturated from methylene chloride/hexanes to give a white solid (5.7 g, 88%).

¹H NMR (CDCl₃) δ 8.13 (d, 1H, J=7.7 Hz), 7.80 (d, 1H, J=7.7 Hz), 7.63~7.71 (m, 2H), 7.18~7.24 (m, 2H), 6.92 (t, 1H, J=7.3 Hz), 6.71 (d, 2H, J=8.0 Hz), 5.90 (br t, 1H, J=5.5 Hz), 4.0 (t, 2H, J=5.1 Hz), 3.52 (t, 2H, 5.5 Hz). MS (ES+) m/e 323 (M+1).

b) N-[(Methoxycarbonyl)methyl]-N-(2-phenoxyethyl)-2-nitrobenzenesulfonamide



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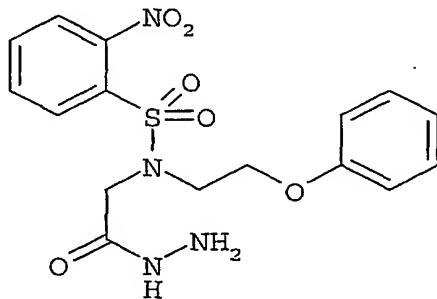
To a stirred mixture of 2-(2-nitrobenzensulfonamido)ethyl phenyl ether (1.61 g, 5 mmol) and potassium carbonate (6.91 g, 50 mmol) in tetrahydrofuran (50 mL) was added sodium iodide (300 mg, 2 mmol) and methyl bromoacetate (1.53 g, 10 mmol) and stirring was continued at room temperature overnight. The mixture was diluted with ethyl acetate

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(25 mL), washed with water (2 x 30 mL) and brine (25 mL), dried (MgSO_4), and concentrated to give yellow oil (1.99 g, 100%).

¹H NMR (CDCl_3) δ 8.08 (d, 1H, $J=8.8$ Hz), 7.60~7.68 (m, 3H), 7.24 (m, 2H), 6.93 (t, 1H, $J=7.3$ Hz), 6.77 (d, 2H, $J=8.8$ Hz), 4.37 (s, 2H), 4.15 (t, 2H, $J=4.8$ Hz), 3.80 (t, 2H, $J=4.8$ Hz), 3.56 (s, 3H). MS (ES+) m/e 395 (M+1).

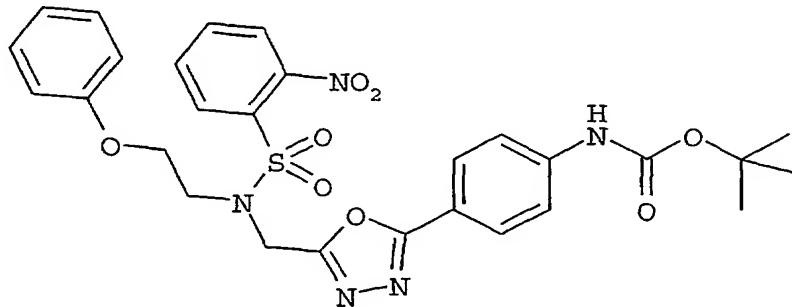
c) 2-[N-(2-phenoxyethyl)-2-nitrobenzenesulfonyl]acetic hydrazide



A mixture of methyl N-[(methoxycarbonyl)methyl]-N-(2-phenoxyethyl)-2-nitrobenzenesulfonamide (1.97 g, 5 mmol) and hydrazine monohydrate (2.5 g, 50 mmol) in ethanol was stirred at room temperature overnight and concentrated. Excess hydrazine was also removed under vacuum. The residue was taken up in ethyl acetate (75 mL) and washed with water (2 x 50 mL), dried (MgSO_4), and concentrated to give a yellow oil (1.73 g, 88%).

¹H NMR (CDCl_3) δ 8.06 (d, 1H, $J=7.7$ Hz), 7.65~7.74 (m, 3H), 7.23~7.27 (m, 2H), 6.95 (t, 1H, $J=7.3$ Hz), 6.80 (d, 2H, $J=8.4$ Hz), 4.15 (t, 2H, $J=5.0$ Hz), 4.12 (s, 2H), 3.81 (t, 2H, $J=5.0$ Hz), 3.56 (s, 3H). MS (ES+) m/e 395 (M+1).

d) 2-{[N-(2-nitrobenzenesulfonyl)-(2-phenoxyethyl)amino]methyl}-5-{4-[(tert-butoxycarbonyl)amino]phenyl}-1,3,4-oxadiazole

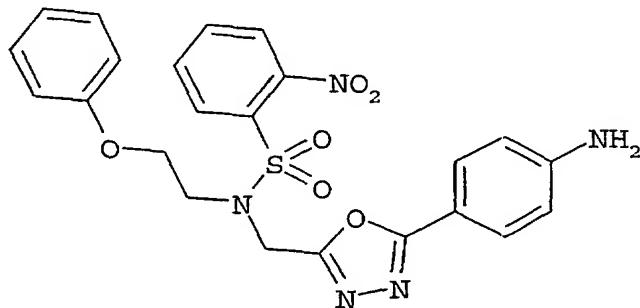


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To a stirred mixture of 2-[N-(2-phenoxyethyl)-2-nitrobenzenesulonamido]acetic hydrazide (1.58 g, 4 mmol), 4-(tert-butyloxycarbonyl)bezoic acid (1.19 g, 5 mmol), and 4-(N,N-dimethylamino)phenyldiphenylphosphine (4.58 g, 15 mmol) in acetonitrile (50 mmol), at 0 °C, was added a solution of triethylamine (2.56 g, 25 mmol) in carbon 5 tetrachloride (3.85 g, 25 mmol). After 10 min the cooling bath was removed and stirring was continued at room temperature overnight. The resultant mixture was concentrated to approximately half the original volume and partitioned between ether (150 mL) and 2 M HCl (100 mL). The organic layer was washed with 2 M HCl (3 x 150 mL) and 2 M NaOH (3 x 50 mL), dried (MgSO_4), and concentrated to give a brown oil (1.81 g, 76%).

10 ^1H NMR (CDCl_3) δ 8.04 (d, 1H, $J=8.8$ Hz), 7.77 (d, 2H, $J=8.8$ Hz), 7.43~7.67 (m, 5H), 7.19 (t, 2H, $J=8.0$ Hz), 6.90 (t, 1H, $J=7.3$ Hz), 6.71 (d, 2H, $J=7.7$ Hz), 5.04 (s, 2H), 4.19 (t, 2H, $J=5.1$ Hz), 3.90 (t, 2H, $J=5.1$ Hz), 1.51 (s, 9H). MS (ES+) m/e 596 (M+1).

15 e) 2-{[N-(2-nitrobenzenesulfonyl)-(2-phenoxyethyl)amino]methyl}-5-(4-aminophenyl)-1,3,4-oxadiazole

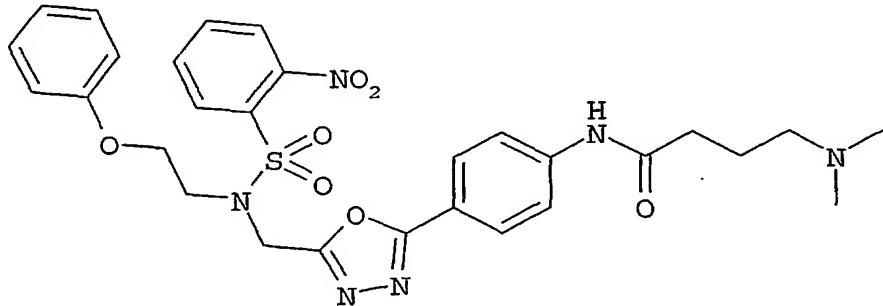


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Trifluoroacetic acid (2.5 mL) was added to a solution of 2-{[N-(2-nitrobenzenesulfonyl)-(2-phenoxyethyl)amino]methyl}-5-{4-[(tert-butoxycarbonyl)amino]phenyl}-1,3,4-oxadiazole (1.19 g, 2 mmol) in methylene chloride (7.5 mL). The mixture was stirred at room temperature for 3 h and concentrated. The residue was dissolved in methylene chloride (15 mL) and washed with 2 M NaOH (15 mL), dried (MgSO_4), and concentrated. The residue was purified by column chromatography (silica gel, ethyl acetate/hexanes) to give a pale yellow oil (400 mg, 40%).

¹H NMR (CDCl_3) δ 8.09 (d, 1H, $J=7.4$ Hz), 7.57~7.66 (m, 5H), 7.22 (m, 2H), 6.90 (t, 1H, $J=7.3$ Hz), 6.71 (d, 2H, $J=8.0$ Hz), 6.65 (d, 2H, $J=8.8$ Hz), 5.01 (s, 2H), 4.18 (t, 2H, $J=5.0$ Hz), 3.90 (t, 2H, $J=5.0$ Hz). MS (ES+) m/e 496 ($M+1$).

f) 2-{[N-(2-nitrobenzenesulfonyl)-(2-phenoxyethyl)amino]methyl}-5-{4-[(4-(N,N-dimethylamino)butanoyl)amino]phenyl}-1,3,4-oxadiazole



15

To a stirred mixture of 2-{[N-(2-nitrobenzenesulfonyl)-(2-phenoxyethyl)amino]methyl}-5-(4-aminophenyl)-1,3,4-oxadiazole (248 mg, 0.5 mmol), 4-(N,N-dimethylamino)butanoic acid hydrochloride (168 mg, 1 mmol), and 1-hydroxybenzotriazole (135 mg, 1 mmol) in N,N-dimethylformamide (5 mL) was added diisopropylcarbodiimide (126 mg, 1 mmol) and stirring was continued at room temperature overnight. The mixture was diluted with ethyl acetate (25 mL), washed with 2 M NaOH (3 x 10 mL), water (2 x 10 mL), and brine (10 mL), dried (MgSO_4), and concentrated. The residue was purified by chromatography (silica gel, 20% methanol/methylene chloride) to give a pale yellow oil (228 mg, 75%).

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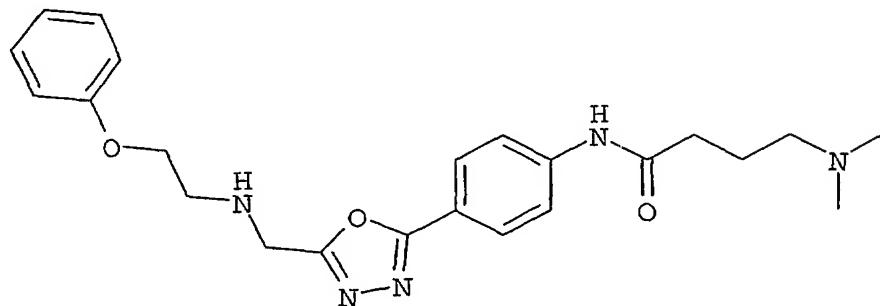
¹H NMR (CDCl_3) δ 10.68 (s, 1H), 8.10 (d, 1H, $J=9.1$ Hz), 7.77 (d, 2H, $J=8.8$ Hz), 7.58~7.65 (m, 5H), 7.19 (m, 2H), 6.90 (t, 1H, $J=7.3$ Hz), 6.71 (d, 2H, $J=7.7$ Hz), 5.04 (s,

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2H), 4.19 (t, 2H, J=4.9 Hz), 3.90 (t, 2H, J=4.9 Hz), 2.49~2.56 (m, 4H), 2.36 (s, 6H), 1.86 (m, 2H). MS (ES+) m/e 609 (M+1).

g) 2-{{(2-phenoxyethyl)amino}methyl}-5-{{4-[(N,N-

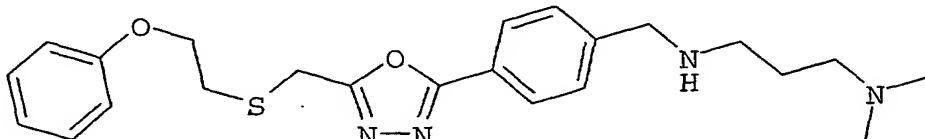
5 dimethylamino)butanoyl]amino}phenyl}-1,3,4-oxadiazole



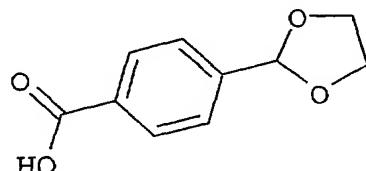
A mixture of 2-{{[N-(2-nitrobenzenesulfonyl)-(2-phenoxyethyl)amino]methyl}-5-{{4-[(N,N-dimethylamino)butanoyl]amino}phenyl}-1,3,4-oxadiazole (152 mg, 0.25 mmol) and potassium carbonate (104 mg, 0.75 mmol) in N,N-dimethylformamide (1.5 mL) was stirred at room temperature and benzenethiol (33 mg, 0.3 mmol) was added. Stirring was continued for 3 h and the mixture was diluted with water (5 mL) and extracted with ethyl acetate (8 mL). The ethyl acetate extract was loaded to a cation exchange column (Bio-Rad 50W-x2 resin) and eluted with methanol. The basic material was recovered by flushing the column with 2 M ammonia in methanol and further purified by preparative TLC (silica gel, 10% methanol/methylene chloride) to give a pale yellow oil (71 mg, 67%).

¹H NMR (CDCl₃) δ 10.59 (s, 1H), 7.95 (d, 1H, J=8.8 Hz), 7.65 (d, 2H, J=8.8 Hz), 7.22~7.26 (m, 2H), 6.92 (t, 1H, J=7.3 Hz), 6.87 (d, 2H, J=8.1 Hz), 4.16 (s, 2H), 4.08 (t, 2H, J=5.0 Hz), 3.11 (t, 2H, J=5.0 Hz), 2.49~2.56 (m, 4H), 2.36 (s, 6H), 1.88 (m, 2H). IR (film, cm⁻¹) 3483, 3340, 2948, 2925, 1661, 1605, 1500, 1428, 1182, 1067, 1027, 756. MS (ES+) m/e 424 (M+1). Anal. Calcd for C₂₃H₂₉N₅O₃: C, 65.23; H, 6.90; N, 16.54. Found C, 65.01; H, 6.96; N, 16.77.

Preparation of 2-{{(2-phenoxyethyl)thio)methyl}-5-{4-[(N',N'-dimethyl-1,3-propanediamino)methyl]phenyl}-1,3,4-oxadiazole



a) 2-[4-(hydroxycarbonyl)phenyl]-1,3-dioxolane

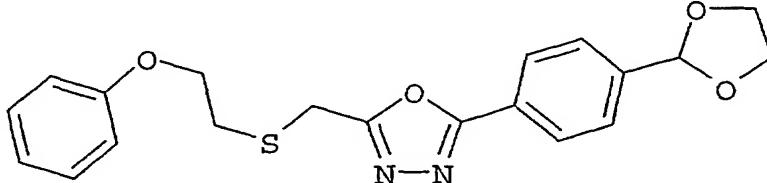


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Aluminum oxide (Brockmann I, basic, 150 mesh, 34 g, 0.33 mol) was added to a solution of 4-carboxybenzaldehyde (20 g, 0.13 mol) and ethylene glycol (83 g, 1.3 mol) in toluene (700 mL). The resulting suspension was refluxed for 24 h. After cooling, the solids were filtered and washed with ethyl acetate (300 mL). The filtrate was extracted with water (10x100 mL), dried ($MgSO_4$), filtered and concentrated to yield 15.9 g (61%) of a white solid that required no further purification.

1H NMR ($CDCl_3$) δ 8.09 (d, 2H, $J=8$ Hz), 7.57 (d, 2H, $J=8$ Hz), 5.86 (s, 1H), 4.07 (m, 4H). MS (ES-) m/e 193 (M-1).

15 b) 2-{{(2-Phenoxyethyl)thio)methyl}-5-[4-(1,3-dioxolan-2-yl)phenyl]-1,3,4-oxadiazole



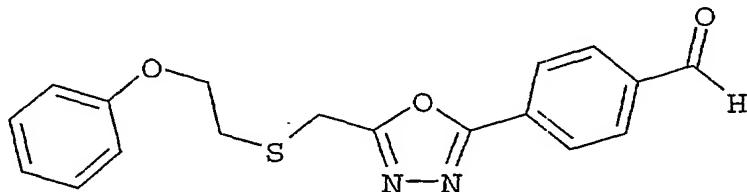
A suspension containing 2-[4-(hydroxycarbonyl)phenyl]-1,3-dioxolane (6.55 g, 33.7 mmol), 2-[(2-phenoxyethyl)thio]acetic acid hydrazide, hydrochloride salt (10.63 g, 20.4 mmol) and 4-(dimethylamino)phenyldiphenylphosphine (30.9 g, 101.1 mmol) was cooled in an ice/water bath. Triethylamine (28.2 mL, 202.3 mmol) and carbon tetrachloride (16.3 mL, 168.6 mmol) were combined and added dropwise over 5 min. The reaction stirred in the bath for 10 min, then stirred at room temperature for 16 h. The

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solution was concentrated to about 10% of its original volume and diluted with ethyl ether (300 mL) and 2 N HCl (200 mL). The organic phase was further extracted with 2 N HCl (6x100 mL), dried (MgSO_4), filtered and concentrated to yield 8 g (62%) of a yellow solid that was not further purified.

5 ^1H NMR (CDCl_3) δ 8.03 (d, 2H, $J=7$ Hz), 7.59 (d, 2H, $J=7$ Hz), 7.24 (m, 2H), 6.88 (m, 3H), 5.85 (s, 1H), 4.20 (m, 2H), 4.12 (m, 2H), 4.07 (m, 2H), 4.04 (m, 2H), 3.04 (m, 2H). MS (ES+) m/e 385 (M+1).

c) 2-{{(2-Phenoxyethyl)thio}methyl}-5-(4-formylphenyl)-1,3,4-oxadiazole



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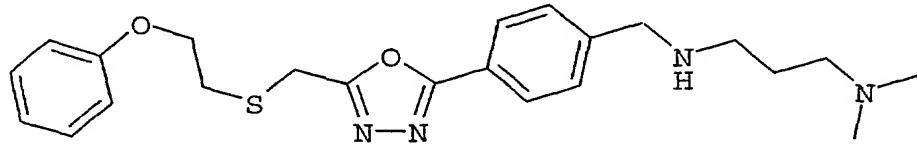
A solution 2-{{(2-phenoxyethyl)thio}methyl}-5-[4-(1,3-dioxolan-2-yl)phenyl]-1,3,4-oxadiazole (8.0 g, 20.8 mmol) and pyridinium p-toluenesulfonate (1.0 g, 4.0 mmol) and water (5 mL) in acetone (200 mL) was refluxed for 6 h, cooled and concentrated. The residue was diluted with ethyl acetate (250 mL) and washed with saturated aqueous sodium bicarbonate (3x60 mL), dried (MgSO_4), filtered and concentrated. This residue was purified over silica gel (25% ethyl acetate/hexanes) to yield 2.22 g (31%) of a white solid.

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^1H NMR (CDCl_3) δ 10.08 (s, 1H), 8.18 (d, 2H, $J=7$ Hz), 7.99 (d, 2H, $J=7$ Hz), 7.26 (m, 2H), 6.93 (m, 1H), 6.87 (d, 2H, $J=8$ Hz), 4.20 (t, 2H, $J=11$ Hz), 4.07 (s, 2H), 3.05 (t, 2H, $J=11$ Hz). MS (ES+) m/e 341 (M+1).

d) 2-{{(2-Phenoxyethyl)thio}methyl}-5-{4-[(N',N'-dimethyl-1,3-propanediamino)methyl]phenyl}-1,3,4-oxadiazole



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A solution of 2-{{(2-phenoxyethyl)thio}methyl}-5-(4-formylphenyl)-1,3,4-oxadiazole (200 mg, 0.59 mmol), 3-(N,N-dimethylamino)propylamine (0.08 mL, 0.64

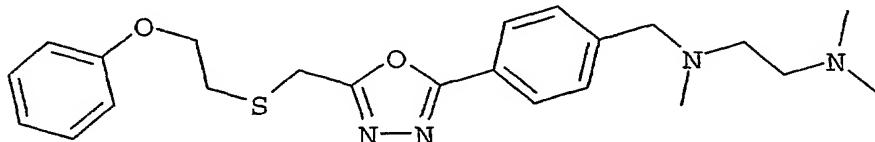
mmol) and glacial acetic acid (0.03 mL, 0.59 mmol) in 1,2-dichloroethane (3.0 mL) was stirred under nitrogen at room temperature. Sodium triacetoxyborohydride (190 mg, 0.88 mmol) was added and the reaction stirred for 5 h. The mixture was then diluted with methylene chloride (5 mL), washed with 2 N NaOH (10 mL), dried (MgSO_4), filtered and concentrated to yield 0.29 g of a pale yellow oil. This material was purified by preparative TLC [90% methylene chloride/5% methanol/5% (2.0 M ammonia/methanol)] to yield 164 mg (66%) of a colorless oil.

¹H NMR (CDCl_3) δ 7.97 (d, 2H, $J=8$ Hz), 7.44 (d, 2H, $J=8$ Hz), 7.25 (m, 2H), 6.93 (m, 1H), 6.87 (d, 2H, $J=8$ Hz), 4.19 (t, 2H, $J=12$ Hz), 4.03 (s, 2H), 3.84 (s, 2H), 3.04 (t, 2H, $J=12$ Hz), 2.68 (t, 2H, $J=14$ Hz), 2.34 (t, 2H, $J=14$ Hz), 2.22 (s, 6H), 1.72 (m, 2H).
MS (ES+) m/e 427 (M+1). IR (film, cm^{-1}) 3458, 3425, 3397, 1640, 1591, 1491, 1241.
Anal. Calcd for $\text{C}_{23}\text{H}_{30}\text{N}_4\text{O}_2\text{S}$: C, 64.76; H, 7.09; N, 13.13; S, 7.52. Found C, 64.40; H, 6.98; N, 13.29; S, 7.80.

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Example 138

Preparation of 2-{{(2-phenoxyethyl)thio)methyl}-5-{{[4-[N,N',N'-trimethyl-1,2-ethanediamino)methyl]phenyl}-1,3,4-oxadiazole



A solution of 2-{{(2-phenoxyethyl)thio)methyl}-5-(4-formylphenyl)-1,3,4-oxadiazole (200 mg, 0.59 mmol), N,N,N'-trimethylethylenediamine (0.15 mL, 1.18 mmol) and glacial acetic acid (0.03 mL, 0.59 mmol) in 1,2-dichloroethane (3.0 mL) was stirred under nitrogen at room temperature. Sodium triacetoxyborohydride (190 mg, 0.88 mmol) was added and the reaction stirred for 3 h. The mixture was then diluted with methylene chloride (5 mL), washed with 2 N NaOH (10 mL), dried (MgSO_4), filtered and concentrated to yield 0.31 g of a pale yellow oil. This material was purified by preparative TLC [90% methylene chloride/5% methanol/5% (2.0 M ammonia/methanol)] to yield 172 mg (69%) of a white solid.

¹H NMR (CDCl_3) δ 7.96 (d, 2H, $J=6$ Hz), 7.44 (d, 2H, $J=6$ Hz), 7.25 (m, 2H), 6.93 (m, 1H), 6.87 (d, 2H, $J=7$ Hz), 4.19 (m, 2H), 4.03 (s, 2H), 3.56 (s, 2H), 3.04 (m, 2H), 2.48

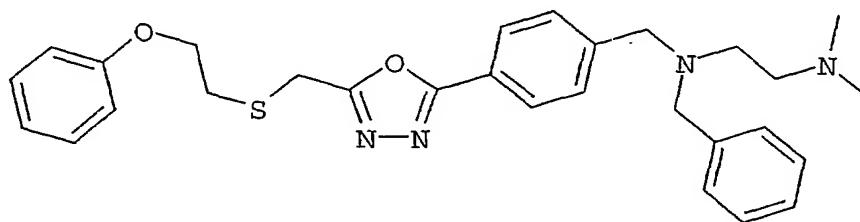
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(m, 4H), 2.24 (s, 3H), 2.22 (s, 6H). IR (KBr, cm⁻¹) 3419, 2945, 2802, 2763, 1594, 1559, 1493, 1460, 1416, 1310, 1237, 1180, 1136, 1083, 1029, 851, 752, 693. MS (ES+) m/e 427 (M+1). Anal. Calcd for C₂₃H₃₀N₄O₂S: C, 64.76; H, 7.09; N, 13.13; S, 7.52. Found C, 64.96; H, 7.01; N, 13.47; S, 7.38.

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Example 139

Preparation of 2-{{(2-phenoxyethyl)thio}methyl}-5-{4-[(N-benzyl-N',N'-dimethyl-1,2-ethanediamino)methyl]phenyl}-1,3,4-oxadiazole

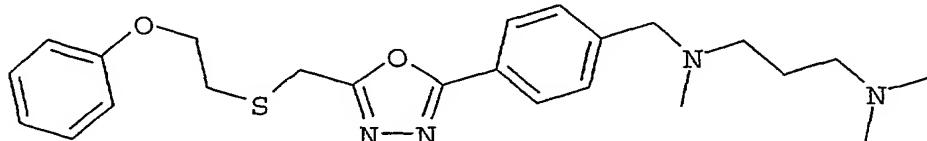


10 A solution of 2-{{(2-phenoxyethyl)thio}methyl}-5-(4-formylphenyl-1,3,4-oxadiazole (144 mg, 0.42 mmol), N'-benzyl-N,N-dimethylethylenediamine (0.16 mL, 0.85 mmol) and glacial acetic acid (0.025 mL, 0.44 mmol) in 1,2-dichloroethane (3.0 mL) was stirred under nitrogen at room temperature. Sodium triacetoxyborohydride (135 mg, 0.64 mmol) was added and the reaction stirred for 4 h. The mixture was then diluted with
15 methylene chloride (5 mL), washed with 2 N NaOH (10 mL), dried (MgSO₄), filtered and concentrated to yield 0.31 g of a pale yellow oil. This material was purified by preparative TLC [90% methylene chloride/5% methanol/5% (2.0 M ammonia/methanol)] to yield 101 mg (47%) of a white solid.

1 H NMR (CDCl₃) δ 7.95 (d, 2H, J=8 Hz), 7.48 (d, 2H, J=8 Hz), 7.32 (m, 5H), 7.27 (m, 2H), 6.92 (m, 1H), 6.87 (d, 2H, J=8 Hz), 4.19 (t, 2H, J=12 Hz), 4.03 (s, 2H), 3.64 (s, 2H), 3.60 (s, 2H), 3.03 (t, 2H, J=12 Hz), 2.58 (dd, 2H, J=7 and 8 Hz), 2.45 (dd, 2H, J=7 and 8 Hz), 2.22 (s, 6H). IR (KBr, cm⁻¹) 3435, 3028, 2970, 2931, 2877, 2793, 1597, 1557, 1496, 1458, 1418, 1364, 1295, 1239, 1170, 1119, 1077, 1018, 971, 836, 746, 694. MS (ES+) m/e 503 (M+1). Anal. Calcd for C₂₉H₃₄N₄O₂S: C, 69.29; H, 6.82; N, 11.15; S, 6.38. Found C, 68.96; H, 6.90; N, 11.15; S, 6.27.

Example 140

Preparation of 2-{[(2-phenoxyethyl)thio]methyl}-5-{4-[(N,N',N'-trimethyl-1,3-propanediamino)methyl]phenyl}-1,3,4-oxadiazole



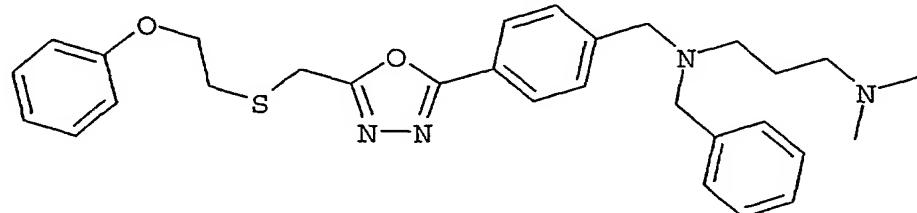
A solution of 2-{[(2-phenoxyethyl)thio]methyl}-5-(4-formylphenyl)-1,3,4-oxadiazole (144 mg, 0.42 mmol), N,N,N'-trimethyl-1,3-propanediamine (0.125 mL, 0.85 mmol) and glacial acetic acid (0.025 mL, 0.44 nmol) in 1,2-dichloro-ethane (3.0 mL) was stirred under nitrogen at room temperature. Sodium triacetoxyborohydride (135 mg, 0.64 mmol) was added and the reaction stirred for 3 h. The mixture was then diluted with methylene chloride (5 mL), washed with 2 N NaOH (10 mL), dried (MgSO_4), filtered and concentrated to yield 0.24 g of a pale yellow oil. This material was purified by preparative TLC [90% methylene chloride/5% methanol/5% (2.0 M ammonia/methanol)] to yield 87 mg (47%) of a colorless oil.

^1H NMR (CDCl_3) δ 7.96 (d, 2H, $J=8$ Hz), 7.43 (d, 2H, $J=8$ Hz), 7.25 (m, 2H), 6.92 (m, 1H), 6.87 (d, 2H, $J=9$ Hz), 4.19 (t, 2H, $J=12$ Hz), 4.03 (s, 2H), 3.52 (s, 2H), 3.03 (t, 2H, $J=12$ Hz), 2.40 (dd, 2H, $J=7$ and 8 Hz), 2.31 (dd, 2H, $J=7$ and 8 Hz), 2.23 (s, 6H), 2.18 (s, 3H), 1.71 (m, 2H). IR (film, cm^{-1}) 3402, 1595, 1491, 1239, 755, 730. MS (ES+) m/e 442 (M+1). Anal. Calcd for $\text{C}_{24}\text{H}_{32}\text{N}_4\text{O}_2\text{S}$: C, 65.42; H, 7.32; N, 12.72; S, 7.28. Found C, 65.68; H, 7.58; N, 12.61; S, 7.23.

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Example 141

Preparation of 2-{[(2-phenoxyethyl)thio]methyl}-5-[4-(N-benzyl-N',N'-dimethyl-1,3-propanediamino)phenyl]-1,3,4-oxadiazole



A solution of 2-{[(2-Phenoxyethyl)thio]methyl}-5-{4-[(N',N'-dimethyl-1,3-propanediamino)methyl]phenyl}-1,3,4-oxadiazole (110 mg, 0.26 mmol), benzaldehyde

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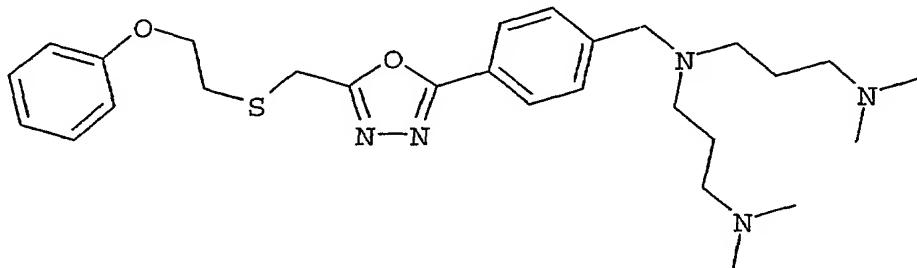
(0.03 mL, 0.28 mmol) and glacial acetic acid (0.015 mL, 0.26 mmol) in 1,2-dichloroethane (3.0 mL) was stirred under nitrogen at room temperature. Sodium triacetoxyborohydride (82 mg, 0.39 mmol) was added and the reaction stirred for 8 h. The mixture was then diluted with methylene chloride (5 mL), washed with 2 N NaOH (10 mL), dried (MgSO_4), filtered and concentrated to yield 0.15 g of a pale yellow oil. This material was purified by preparative TLC [90% methylene chloride/5% methanol/5% (2.0 M ammonia/methanol)] to yield 52 mg (39%) of a white solid.

¹H NMR (CDCl_3) δ 7.95 (d, 2H, $J=8$ Hz), 7.47 (d, 2H, $J=8$ Hz), 7.32 (m, 5H), 7.28 (m, 2H), 6.92 (m, 1H), 6.87 (d, 2H, $J=8$ Hz), 4.18 (t, 2H, $J=12$ Hz), 4.03 (s, 2H), 3.59 (s, 2H), 3.56 (s, 2H), 3.03 (t, 2H, $J=12$ Hz), 2.45 (dd, 2H, $J=7$ and 8 Hz), 2.24 (m, 2H), 2.17 (s, 6H), 1.68 (m, 2H). IR (KBr, cm^{-1}) 3434, 3026, 2934, 2874, 2785, 2357, 1597, 1558, 1495, 1456, 1419, 1369, 1297, 1239, 1173, 1118, 1075, 1020, 967, 830, 745, 693. MS (ES+) m/e 518 (M+1). Anal. Calcd for $\text{C}_{30}\text{H}_{36}\text{N}_4\text{O}_2\text{S}$: C, 69.74; H, 7.02; N, 10.84; S, 6.21. Found C, 69.65; H, 6.96; N, 10.67; S, 6.39.

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Example 142

Preparation of 2-{{(2-phenoxyethyl)thio)methyl}-5-{4-[(N,N-bis-(3-(N',N'-dimethyl)propyl)amino)methyl]phenyl}-1,3,4-oxadiazole



20 A solution of 2-{{(2-phenoxyethyl)thio)methyl}-5-(4-formylphenyl)-1,3,4-oxadiazole (163 mg, 0.48 mmol), 3,3'-iminobis-(N,N-dimethylpropylamine) (0.22 mL, 0.99 mmol) and glacial acetic acid (0.03 mL, 0.52 mmol) in 1,2-dichloroethane (4.0 mL) was stirred under nitrogen at room temperature. Sodium triacetoxyborohydride (153 mg, 0.72 mmol) was added and the reaction stirred for 16 h. The mixture was then diluted 25 with methylene chloride (10 mL), washed with 2 N NaOH (10 mL), dried (MgSO_4), filtered and concentrated to yield 0.35 g of a pale yellow oil. Half of this material was

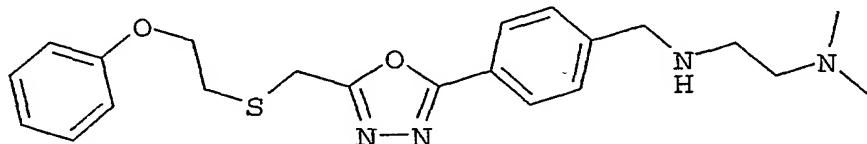
purified by preparative TLC [90% methylene chloride/5% methanol/5% (2.0 M ammonia-methanol)] to yield 84 mg (34%) of a white solid.

¹H NMR (CDCl₃) δ 7.94 (d, 2H, J=8 Hz), 7.43 (d, 2H, J=8 Hz), 7.25 (m, 2H), 6.90 (m, 1H), 6.88 (d, 2H, J=8 Hz), 4.19 (t, 2H, J=12 Hz), 4.03 (s, 2H), 3.59 (s, 2H), 3.04 (t, 2H, J=12 Hz), 2.44 (t, 4H, J=15 Hz), 2.26 (t, 4H, J=15 Hz), 2.20 (s, 12H), 1.63 (m, 4H). IR (KBr, cm⁻¹) 3430, 2939, 2889, 2863, 2812, 2770, 2720, 1599, 1562, 1497, 1461, 1380, 1297, 1242, 1173, 1082, 1027, 826, 751, 691. MS (ES+) m/e 513 (M+1). Anal. Calcd for C₂₈H₄₁N₅O₂S: C, 65.72; H, 8.08; N, 13.68; S, 6.26. Found C, 65.19; H, 8.10; N, 13.39; S, 6.28.

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Example 143

Preparation of 2-{[(2-phenoxyethyl)thio]methyl}-5-{4-[(N',N'-dimethyl-1,2-ethanediamino)methyl]phenyl}-1,3,4-oxadiazole



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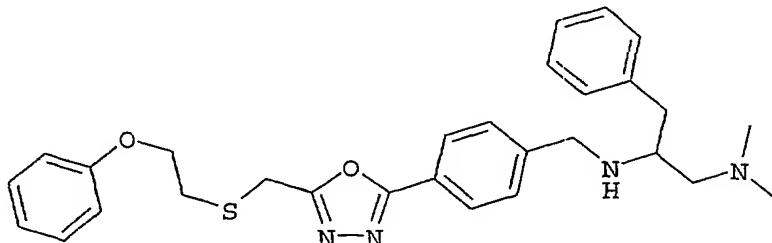
A solution of 2-{[(2-phenoxyethyl)thio]methyl}-5-(4-formylphenyl)-1,3,4-oxadiazole (340 mg, 1.0 mmol), N,N-dimethyl-1,2-ethylenediamine (0.22 mL, 2.0 mmol) and glacial acetic acid (0.06 mL, 1.0 mmol) in 1,2-dichloroethane (6.0 mL) was stirred under nitrogen at room temperature. Sodium triacetoxyborohydride (320 mg, 1.5 mmol) was added and the reaction stirred for 16 h. The mixture was then diluted with methylene chloride (10 mL), washed with 2 N NaOH (10 mL), dried (MgSO₄), filtered and concentrated to yield 0.43 g of a pale yellow oil. This material was purified by preparative TLC [90% methylene chloride/5% methanol/5% (2.0 M ammonia/methanol)] to yield 154 mg (37%) of a white solid.

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¹H NMR (CDCl₃) δ 7.97 (d, 2H, J=8 Hz), 7.45 (d, 2H, J=8 Hz), 7.25 (m, 2H), 6.93 (m, 1H), 6.87 (d, 2H, J=8 Hz), 4.19 (t, 2H, J=12 Hz), 4.03 (s, 2H), 3.86 (s, 2H), 3.04 (t, 2H, J=12 Hz), 2.67 (t, 2H, J=12 Hz), 2.43 (t, 2H, J=12 Hz), 2.20 (s, 6H). IR (KBr, cm⁻¹) 3423, 3318, 2970, 2928, 2856, 2812, 2781, 1595, 1560, 1492, 1461, 1418, 1237, 1079, 1019, 818, 757, 697. MS (ES+) m/e 414 (M+1). Anal. Calcd for C₂₂H₂₈N₄O₂S: C, 64.05; H, 6.84; N, 13.58; S, 7.77. Found C, 64.32; H, 6.24; N, 13.52; S, 7.60.

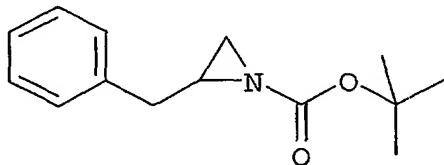
Example 144

Preparation of (+)-2-{{(2-phenoxyethyl)thio]methyl}-5-{4-[((1-benzyl-2-(N,N-dimethylamino)ethyl)amino)methyl]phenyl}-1,3,4-oxadiazole



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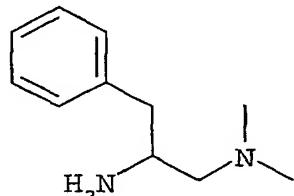
a) (+)-N-(tert-Butyloxycarbonyl)-2-benzylaziridine



A solution of (+)-2-amino-3-phenylpropanol (6g, 40 mmol) and di-t-butyl dicarbonate (9.53 g, 44 mmol) in isopropyl alcohol (20 mL) and 1,4-dioxane (40 mL) was stirred at room temperature for 4 h. The reaction was concentrated and vacuum dried. This material, p-toluenesulfonyl chloride (9.2 g, 48 mmol) and potassium hydroxide (9.0g, 160 mmol) were stirred in ethyl ether (400 mL) at room temperature for 20 h. The mixture was then poured into ice water (400 mL). The aqueous material was extracted with ethyl ether (300 mL) and the combined organic fractions were dried (MgSO_4), filtered and concentrated to yield 9.0 g (97%) of a colorless oil.

$^1\text{H NMR}$ (CDCl_3) δ 7.25 (m, 5H), 2.95 (m, 1H), 2.60 (m, 2H), 2.33 (m, 1H), 2.00 (m, 1H), 1.42 (s, 9H). MS (ES+) m/e 134 ($\text{M}+1\text{-Boc}$).

b) (+)-N,N-Dimethyl-2-amino-3-phenylpropylamine



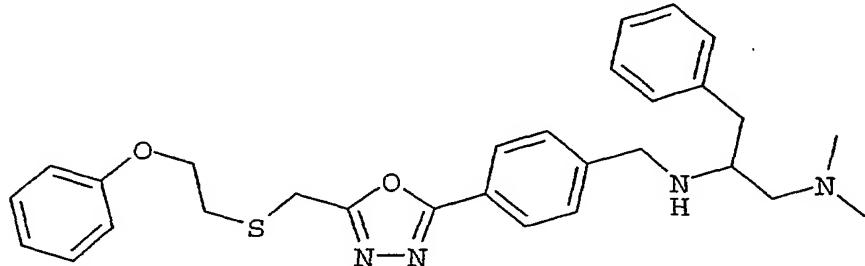
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A solution of (+)-N-boc-2-benzylaziridine (3.0 g, 12.9 mmol) and dimethylamine (2.0 M in THF, 50 mL, 100 mmol) in anhydrous acetonitrile (20 mL) was split among three sealed tubes and refluxed for 20 h. The mixture was concentrated to yield 4.0 g of an orange oil. This material was dissolved in methanol (20 mL) and loaded onto a 5 column containing Bio-Rad 50W-X2 cationic exchange resin (60 g, pre-washed with 800 mL of methanol). The column was washed with methanol (800 mL) and methylene chloride (200 mL). The product was eluted with 2.0 N ammonia/methanol (400 mL) and concentrated to yield 3.2 g (89%) of an orange oil. This product was dissolved in 25% trifluoroacetic acid/methylene chloride (40 mL) and stirred at room temperature for 16 h. 10 The reaction was concentrated, dissolved in methanol (5 mL) and added dropwise to 2N HCl in ethyl ether to generate a solid hydrochloride salt, but the result was a thick oil which would not crystallize. This mixture was then concentrated, dissolved in methanol (20 mL) and loaded onto another column of 50W-X2 resin (50 g), described above. The product was isolated (1.86 g, 91% yield) as a yellow oil.

15 ^1H NMR (CDCl_3) δ 7.17-7.30 (m, 5H), 3.12 (m, 1H), 2.72 (dd, 1H, $J=5$ and 9 Hz), 2.45 (dd, 1H, $J=5$ and 9 Hz), 2.21 (s, 6H), 2.14 (m, 2H). MS (ES+) m/e 179 (M+1).

c) (+)-2-{[(2-Phenoxyethyl)thio]methyl}-5-{4-[(1-benzyl-2-(N,N-dimethylamino)ethyl)amino)methyl]phenyl}-1,3,4-oxadiazole



20 A solution of 2-{[(2-phenoxyethyl)thio]methyl}-5-(4-formylphenyl)-1,3,4-oxadiazole (205 mg, 0.6 mmol), (+)-N,N-dimethyl-2-amino-3-phenylpropylamine hydrochloride salt (430 mg, 2.0 mmol) and glacial acetic acid (0.06 mL, 1 mmol) in 1,2-dichloroethane (8 mL) was stirred under nitrogen at room temperature. Sodium triacetoxyborohydride (191 mg, 0.9 mmol) was added and the reaction stirred for 2 h. The mixture was diluted with methylene chloride (10 mL), extracted with 2 N NaOH (10 mL), dried (MgSO_4), filtered and concentrated to yield 483 mg of an orange oil. This oil 25

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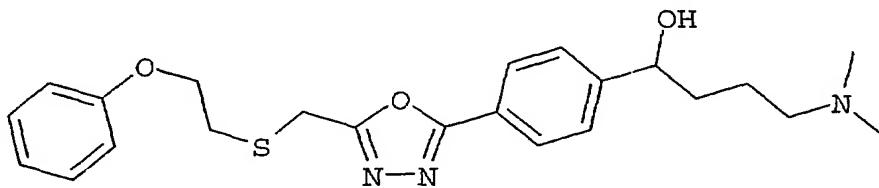
was purified by preparative TLC [90% methylene chloride/5% methanol/5% (2.0 N ammonia in methanol)] to yield 98 mg (32%) of a solid.

¹H NMR (CDCl₃) δ 7.94 (d, 2H, J=8 Hz), 7.36 (d, 2H, J=8 Hz), 7.25 (m, 5H), 7.18 (m, 1H), 7.14 (d, 2H, J=8 Hz), 6.93 (dd, 1H, J=7 and 8 Hz), 6.88 (d, 2H, J=9 Hz), 4.19 (t, 5 H), 4.03 (s, 2H), 3.78 (dd, 2H, J=14 and 14 Hz), 3.04 (t, 2H, J=12 Hz), 2.82 (m, 1H), 2.61 (m, 1H), 2.29 (m, 1H), 2.08 (s, 6H), 2.05 (m, 1H). IR (KBr, cm⁻¹) 3027, 2978, 2933, 2885, 2853, 2816, 2777, 1599, 1562, 1495, 1454, 1359, 1289, 1244, 1167, 1121, 1078, 1025, 976, 835, 803, 749, 696, 512. MS (ES+) m/e 503 (M+1). Anal. Calcd for C₂₉H₃₄N₄O₂S: C, 69.29; H, 6.82; N, 11.15; S, 6.38. Found C, 69.65; H, 6.84; N, 10 10.90; S, 6.22.

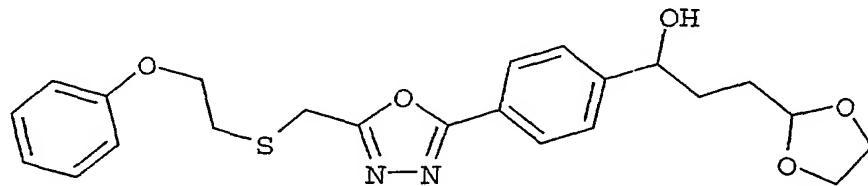
Example 145

Preparation of (+)-2-{[(2-phenoxyethyl)thio]methyl}-5-{4-[4-(N,N-dimethylamino)-1-hydroxybutyl]phenyl}-1,3,4-oxadiazole

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a) (+)-2-{[(2-Phenoxyethyl)thio]methyl}-5-{4-[3-(1,3-dioxolan-2-yl)-1-hydroxypropyl]phenyl}-1,3,4-oxadiazole

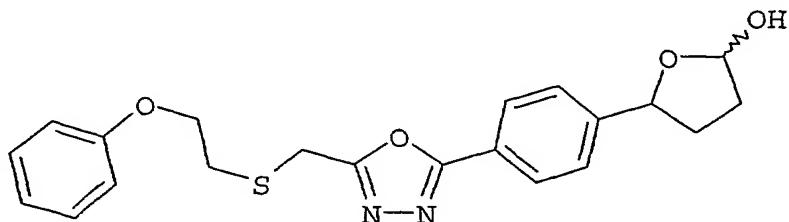


A mixture of 1,2-dibromoethane (0.09 mL, 1 mmol) and magnesium turnings (243 mg, 10 mmol) in anhydrous tetrahydrofuran (5 mL) was cooled in an ice water bath under nitrogen. A solution of 2-(2-bromoethyl)-1,3-dioxolane (1.5 mL, 12.5 mmol) in tetrahydrofuran (1 mL) was added dropwise and the mixture stirred in the cooling bath for 10 min. The mixture was then stirred at room temperature until the magnesium had gone into solution (50 min). After cooling in a dry ice/isopropanol bath, a solution of 2-{[(2-phenoxyethyl)thio]methyl}-5-(4-formylphenyl)-1,3,4-oxadiazole in tetrahydrofuran (5 mL) was added dropwise and stirred for 2 h in the cooling bath. The reaction was

quenched with saturated aqueous ammonium chloride (20 mL) and extracted with ethyl acetate (3x20 mL). The organic material was extracted with brine (25 mL), dried (MgSO_4), filtered and concentrated to yield 1.56 g of a pale yellow oil. This oil was purified by silica gel (50% ethyl acetate/hexanes) to yield 781 mg (88%) of an oil.

5 ^1H NMR (CDCl_3) δ 7.98 (d, 2H, $J=8$ Hz), 7.47 (d, 2H, $J=8$ Hz), 7.24 (m, 1H), 6.93 (dd, 1H, $J=6$ and 7 Hz), 6.87 (d, 2H, $J=7$ Hz), 4.91 (t, 1H, $J=8$ Hz), 4.81 (m, 1H), 4.19 (t, 2H, $J=12$ Hz), 4.03 (s, 2H), 3.95 (m, 2H), 3.86 (m, 2H), 3.03 (t, 2H, $J=12$ Hz), 2.85 (d, 1H, $J=4$ Hz), 1.89 (m, 2H), 1.82 (m, 2H). MS (ES+) m/e 443 (M+1).

10 b) (+)-2-{[(2-Phenoxyethyl)thio]methyl}-5-[4-(5-hydroxy-2,3,4,5-tetrahydrofuran-2-yl)phenyl]-1,3,4-oxadiazole, mixture of cis- and trans-isomers

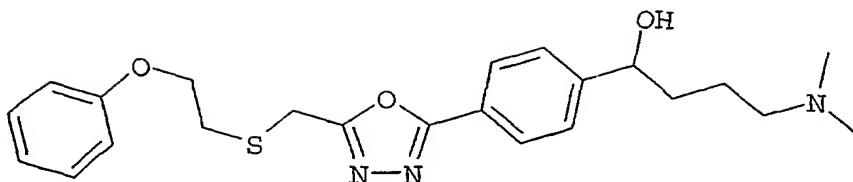


15 A mixture of (+)-2-{[(2-Phenoxyethyl)thio]methyl}-5-[4-[3-(1,3-dioxolan-2-yl)-1-hydroxypropyl]phenyl]-1,3,4-oxadiazole (658 mg, 1.49 mmol) and iron (III) chloride hexahydrate (1.41 g, 5.21 mmol) in methylene chloride (30 mL) was stirred at room temperature for 1 h. The reaction was quenched with saturated aqueous sodium bicarbonate (25 mL) and extracted with methylene chloride (3x25 mL). The organic material was washed with brine (4x20 mL), dried (MgSO_4), filtered and concentrated to yield 498 mg of an orange oil. This oil was purified by preparative TLC (50% ethyl acetate/hexanes to yield 103 mg (17%) of a colorless oil.

20 ^1H NMR (CDCl_3) δ 7.99 (d, 2H, $J=8$ Hz), 7.52 (d, 1H, $J=8$ Hz), 7.42 (d, 1H, $J=8$ Hz), 7.24 (m, 1H), 6.93 (dd, 1H, $J=7$ and 8 Hz), 6.87 (d, 2H, $J=7$ Hz), [cis/trans protons: 5.79 (m, 0.5H), 5.66 (m, 0.5H), 5.29 (m, 0.5H), 5.06 (m, 0.5H)], 4.19 (t, 2H, $J=12$ Hz), 4.03 (s, 2H), 3.04 (t, 2H, $J=12$ Hz), 2.73 (br s, 0.5H), 2.56 (br s, 0.5H), 2.33-2.54 (m, 1H), 1.96-2.18 (m, 2H), 1.76 (m, 1H). MS (ES+) m/e 399 (M+1).

c) (+)-2-{[(2-phenoxyethyl)thio]methyl}-5-{4-[4-(N,N-dimethylamino)-1-hydroxybutyl]phenyl}-1,3,4-oxadiazole

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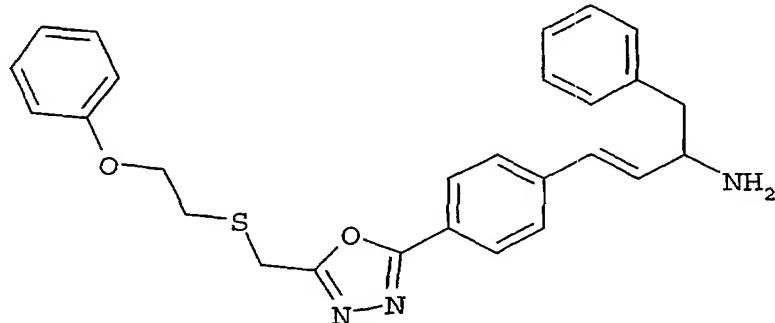


A solution of cis- and trans-(+)-2-{[(2-phenoxyethyl)thio]methyl}-5-[4-(5-hydroxy-2,3,4,5-tetrahydrofuran-2-yl)phenyl]-1,3,4-oxadiazole (100 mg, 0.25 mmol), dimethylamine (2.0 M in THF, 2 mL, 4 mmol) and glacial acetic acid (0.02 mL, 0.35 mmol) in 1,2-dichloroethane was stirred under nitrogen. Sodium triacetoxyborohydride (160mg, 0.76 mmol) was added and the reaction stirred at room temperature for 16 h. The mixture was diluted with methylene chloride (10 mL) and extracted with 2N NaOH (10 mL), dried (MgSO_4), filtered and concentrated to yield 210 mg of an orange oil. This oil was purified by preparative TLC [90% methylene chloride/5% methanol/5% (2.0 N ammonia in methanol)] to yield 35 mg (33%) of a white solid.

^1H NMR (CDCl_3) δ 7.97 (d, 2H, $J=8$ Hz), 7.51 (d, 2H, $J=8$ Hz), 7.24 (m, 2H), 6.92 (dd, 1H, $J=7$ and 8 Hz), 6.87 (d, 2H, $J=8$ Hz), 4.72 (d, 1H, $J=6$ Hz), 4.19 (t, 2H, $J=12$ Hz), 4.03 (s, 2H), 3.47 (s, 1H), 3.03 (t, 2H, $J=12$ Hz), 2.42 (m, 2H), 2.32 (s, 6H), 1.99 (m, 2H), 1.75-1.86 (m, 2H). IR (KBr, cm^{-1}) 3407, 3167, 3093, 3058, 2916, 2868, 2794, 2734, 1594, 1562, 1493, 1464, 1414, 1293, 1236, 1171, 1078, 1013, 838, 755, 696. MS (ES+) m/e 428 (M+1). Anal. Calcd for $\text{C}_{23}\text{H}_{29}\text{N}_3\text{O}_3\text{S}$: C, 64.61; H, 6.84; N, 9.83; S, 7.50. Found C, 64.66; H, 6.41; N, 9.31; S, 7.30.

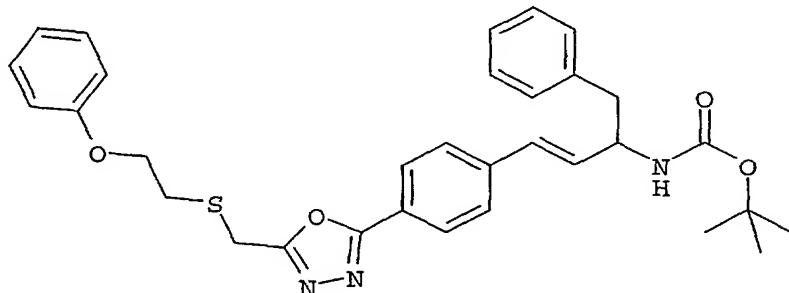
Example 146

Preparation of (E)-2-{[(2-Phenoxyethyl)thio]methyl}-5-[4-(3-amino-3-benzylpropen-1-yl)phenyl]-1,3,4-oxadiazole



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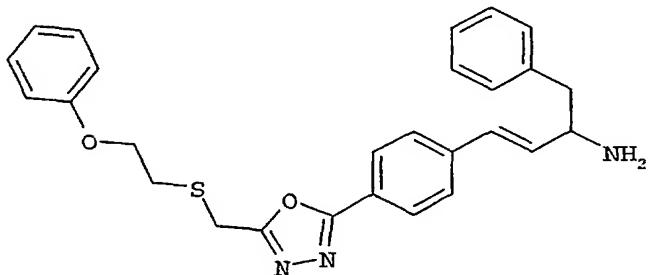
- a) 2-{{(2-Phenoxyethyl)thio}methyl}-5-{4-[3-benzyl-3-(tert-butoxycarbonylamino)propen-1-yl]phenyl}-1,3,4-oxadiazole



A mixture of 2-{{(2-phenoxyethyl)thio}methyl}-5-(4-formylphenyl)-1,3,4-oxadiazole (510 mg, 1.5 mmol), 1-(tert-butoxycarbonyl)-2-benzylaziridine (R- or S-isomer, 933 mg, 4 mmol), and triphenylphosphine (1.05 g, 4 mmol) in 2-propanol (2 mL) was stirred in a sealed tube at 95~100 °C (bath temperature) for 3 days. The reaction mixture was concentrated and purified by chromatography (silica gel, EtOAc/hexanes 1:5). The isolated product was triturated from methylene chloride and hexanes to give pure E-olefines: R-isomer (210 mg, 25%), S-isomer (241 mg, 29%).

¹H NMR (CDCl₃) δ 7.93 (d, 2H, J=8.4 Hz), 7.40 (d, 2H, J=8.1 Hz), 7.18~7.31 (m, 7H), 6.93 (t, 1H, J=7.3 Hz), 6.87 (d, 2H, J=7.6 Hz) 6.46 (d, 1H, J=16.1 Hz), 6.25 (dd, 1H, J=16.1, 5.6 Hz), 4.52~4.65 (m, 2H), 4.19 (t, 2H, J=6.1 Hz), 4.03 (s, 2H), 3.04 (t, 2H, J=6.1 Hz), 2.93 (d, 2H, J=6.3 Hz), 1.40 (s, 9H). IR (KBr, cm⁻¹) 3014, 2949, 2796, 2251, 1688, 1598, 1553, 1326, 1243, 926, 744, 651. MS (ES+) m/e 558 (M+1). Anal. Calcd for C₃₂H₃₅N₃O₄S: C, 68.92; H, 6.33; N, 7.53; S, 5.75. Found R-isomer, C, 68.84; H, 6.35; N, 7.44; S, 5.82; S-isomer, C, 68.88; H, 6.27; N, 7.36; S, 5.79.

- b) 2-{{(2-Phenoxyethyl)thio}methyl}-5-[4-(3-amino-3-benzylpropen-1-yl)phenyl]-1,3,4-oxadiazole



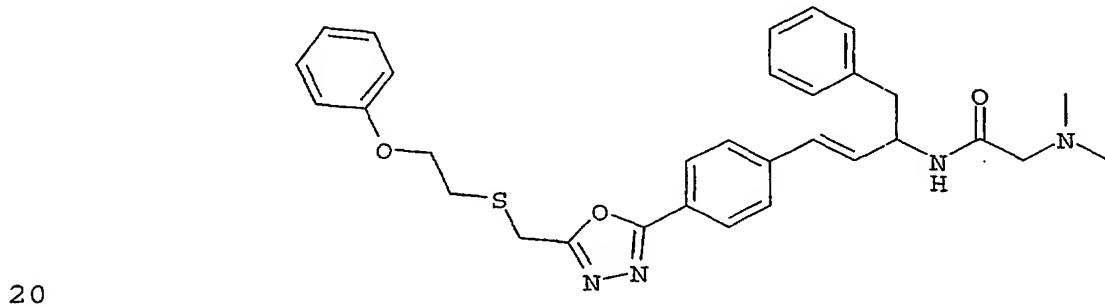
-300-

Trifluoroacetic acid (0.5 mL) was added to a solution of 2-{{(2-Phenoxyethyl)thio]methyl}-5-{4-[3-benzyl-3-(tert-butoxycarbonylamino)propen-1-yl]phenyl}-1,3,4-oxadiazole (139 mg, 0.25 mmol) in methylene chloride (2 mL). The resultant mixture was stirred at room temperature overnight, concentrated, and partitioned between methylene chloride (20 mL) and 2 M NaOH (5 mL). The organic layer was dried (MgSO_4), concentrated and purified by chromatography (silica gel, 5% methanol/methylene chloride) to give a pale yellow solid: R-isomer, 87 mg, 76%; S-isomer, 80 mg, 70%.

¹H NMR (CDCl_3) δ 7.93 (d, 2H, $J=8.5$ Hz), 7.44 (d, 2H, $J=8.4$ Hz), 7.21~7.32 (m, 10 7H), 6.93 (t, 1H, $J=7.3$ Hz), 6.87 (d, 2H, $J=7.7$ Hz) 6.53 (d, 1H, $J=16.1$ Hz), 6.36 (dd, 1H, $J=15.8$, 6.6 Hz), 4.19 (t, 2H, $J=6.2$ Hz), 4.03 (s, 2H), 3.81 (m, 1H), 3.04 (t, 2H, $J=6.2$ Hz), 2.93 (dd, 2H, $J=13.3$, 5.3 Hz), 2.73 (dd, 1H, $J=13.3$, 8.2 Hz). IR (KBr, cm^{-1}) 3028, 2935, 2866, 2830, 1601, 1560, 1494, 1464, 1221, 1050, 915, 733, 700. MS (ES+) m/e 458 (M+1). Anal. Calcd for $\text{C}_{27}\text{H}_{27}\text{N}_3\text{O}_2\text{S}$: C, 70.87; H, 5.95; N, 9.18; S, 7.01. Found R-isomer, C, 70.52; H, 5.93; N, 9.03; S, 7.28; S-isomer, C, 70.94; H, 5.88; N, 9.12; S, 7.00.

Example 147

Preparation of (E)-2-{{(2-Phenoxyethyl)thio]methyl}-5-{4-[3-benzyl-3-(2-(N,N-dimethylamino)acetamido)propen-1-yl]phenyl}-1,3,4-oxadiazole



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A mixture of 2-{{(2-Phenoxyethyl)thio]methyl}-5-{4-(3-amino-3-benzylpropen-1-yl)phenyl}-1,3,4-oxadiazole (46 mg, 0.1 mmol) and N,N-dimethylglycine (20 mg, 0.2 mmol) in pyridine (1 mL), under nitrogen, was cooled to -10~-5 °C (ice-salt bath) and phosphorus oxychloride (0.05 mL, 0.5 mmol) was added. The mixture was stirred at -25 10~-5 °C for 90 min and water (2 mL), followed by ethyl acetate (25 mL), was added. The mixture was washed with 2 M NaOH (2 x 5 mL), water (3 x 10 mL), and brine (10 mL), dried (MgSO_4), and concentrated. The residue was co-evaporated with toluene (20

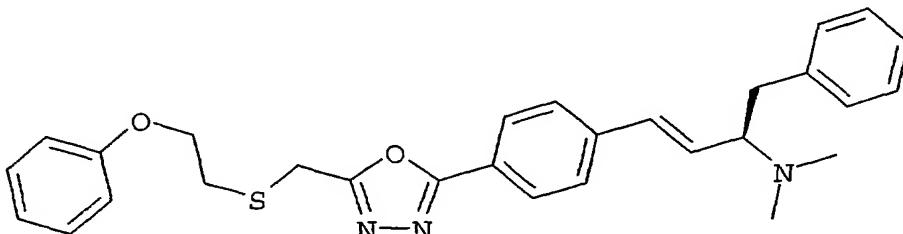
mL) under reduced pressure and purified by preparative TLC (silica gel, 5% methanol/methylene chloride) to give a white solid: R-isomer, 34 mg, 62%; S-isomer, 35 mg, 65%.

¹H NMR (CDCl₃) δ 7.93 (d, 2H, J=8.5 Hz), 7.41 (d, 2H, J=8.5 Hz), 7.19~7.30 (m, 7H), 6.93 (t, 1H, J=7.3 Hz), 6.87 (d, 2H, J=7.7 Hz) 6.49 (d, 1H, J=16.1 Hz), 6.29 (dd, 1H, J=16.1, 6.2 Hz), 4.95 (m, 1H), 4.19 (t, 2H, J=6.2 Hz), 4.03 (s, 2H), 3.04 (t, 2H, J=6.2 Hz), 2.82~3.06 (m, 4H), 2.18 (s, 6H). IR (KBr, cm⁻¹) 3402, 3025, 2958, 2855, 2799, 2776, 1688, 1597, 1550, 1494, 1481, 1239, 1058, 980, 751. MS (ES+) m/e 543 (M+1). Anal. Calcd for C₃₁H₃₄N₄O₃S: C, 68.61; H, 6.31; N, 10.32; S, 5.91. Found R-isomer C, 68.88; H, 6.27; N, 10.25; S, 5.74; S-isomer C, 68.78; H, 6.22; N, 10.24; S, 5.92.

Example 148

Preparation of (R)-(E)-2-{{[(2-phenoxyethyl)thio]methyl}-5-{4-[3-benzyl-3-(N,N-dimethylamino)propen-1-yl]phenyl}-1,3,4-oxadiazole

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A solution containing (R)-(E)-2-{{[(2-phenoxyethyl)thio]methyl}-5-{4-[3-benzyl-3-aminopropen-1-yl]phenyl}-1,3,4-oxadiazole (258 mg, 0.56 mmol) and paraformaldehyde (170 mg, 5.6 mmol) in methanol (6.0 mL) was refluxed for 3h. The mixture was cooled and sodium cyanoborohydride (107 mg, 1.70 mmol) was added; the reaction stirred at room temperature for 2 h. The mixture was diluted with water (10 mL) and the methanol was removed in vacuo. Saturated aqueous sodium bicarbonate (10 mL) was added and the mixture was extracted with methylene chloride (3x15 mL). The organic material was dried (MgSO₄), filtered and concentrated to yield 355 mg of an orange oil. This oil was purified by preparative TLC (10% methanol/methylene chloride) to yield 163 mg (59%) of a pale yellow oil.

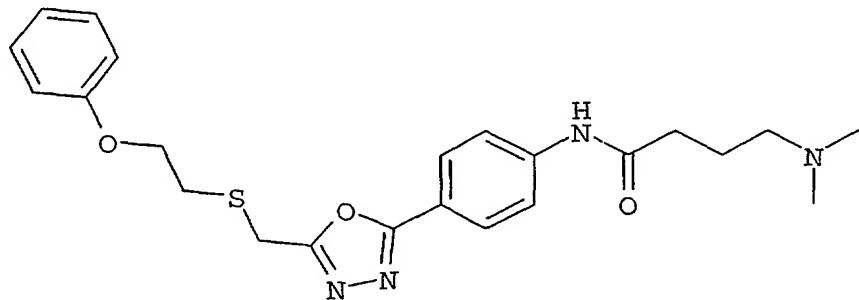
¹H NMR (CDCl₃) δ 7.91 (d, 2H, J=9 Hz), 7.35 (d, 2H, J=8 Hz), 7.24 (m, 5H), 7.13 (m, 2H), 6.93 (dd, 1H, J=7 and 8 Hz), 6.87 (d, 2H, J=8 Hz), 4.18 (t, 2H, J=12 Hz), 4.03 (s, 2H), 3.20 (m, 1H), 3.11 (dd, 2H, J=4 and 9 Hz), 3.03 (t, 2H, J=12 Hz), 2.75 (dd, 2H,

$J=4$ and 9 Hz), 2.37 (s, 6H). IR (film, cm^{-1}) 3030, 2935, 2865, 2823, 2779, 1599, 1557, 1494, 1462, 1239, 1078, 1031, 910, 733, 699. MS (ES+) m/e 486 ($M+1$). Anal. Calcd for $C_{29}\text{H}_{31}\text{N}_3\text{O}_2\text{S}$: C, 71.72; H, 6.43; N, 8.65; S, 6.60. Found C, 71.26; H, 6.21; N, 8.54; S, 6.53.

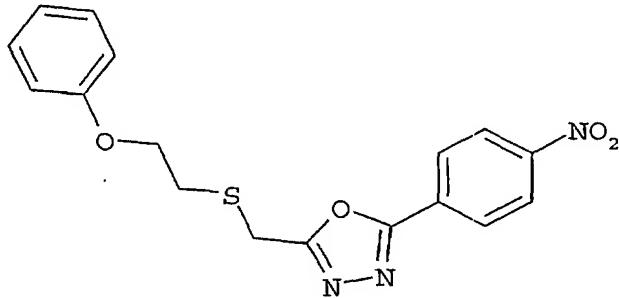
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Example 149

Preparation of 2-{{(2-Phenoxyethyl)thio}methyl}-5-{4-[(4-(N,N-dimethylamino)butanoyl)amino]phenyl}-1,3,4-oxadiazole



10 a) 2-{{(2-Phenoxyethyl)thio}methyl}-5-(4-nitrophenyl)-1,3,4-oxadiazole



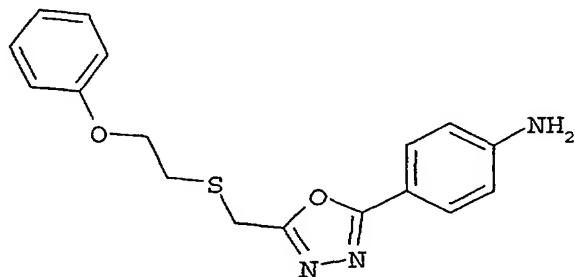
A mixture of 4-nitrobenzoic hydrazide (4.35 g, 24 mmol), 2-(2-phenoxyethylthio)acetic acid (4.25 g, 20 mmol), and (4-N,N-dimethylaminophenyl)diphenylphosphine (18.32 g, 60 mmol) in acetonitrile (200 mL) was stirred and cooled with an ice bath. A mixture of triethylamine (10.12 g, 100 mmol) and carbon tetrachloride (15.38 g, 100 mmol) was added dropwise over 5 min. The cooling was maintained for additional 10 min and removed, and the mixture was allowed to stir overnight. The resultant mixture was concentrated to approximately half the original volume. Diethyl ether (50 mL) and 2 N HCl (300 mL) were added and the mixture was swirled until all solid was dispersed. The solid was collected by filtration and transferred to a beaker. 2 M HCl (300 mL) was added and the mixture was stirred

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until finely dispersed. The solid was collected by filtration and similarly washed again with 2M HCl (300 mL), followed by water (300 mL). The solid was air-dried to give a light tan powder (5.01 g, 70%).

¹H NMR (CDCl₃) δ 8.33 (d, 2H, J=9.2 Hz), 8.18 (d, 2H, J=9.2 Hz), 7.22~7.26 (m, 2H), 6.93 (t, 1H, J=7.3 Hz), 6.86 (d, 2H, J=7.7 Hz), 4.20 (t, 2H, J=6.1 Hz), 4.08 (s, 2H), 3.05 (t, 2H, J=6.0 Hz). MS (ES+) m/e 358 (M+1).

b) 2-{{(2-Phenoxyethyl)thio}methyl}-5-(4-aminophenyl)-1,3,4-oxadiazole

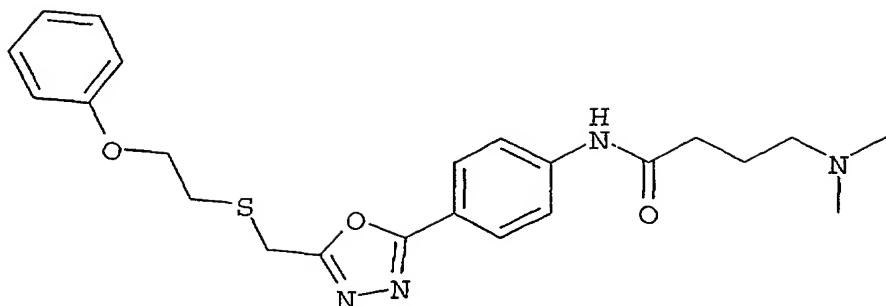


A mixture of 2-{{(2-phenoxyethyl)thio}methyl}-5-(4-nitrophenyl)-1,3,4-oxadiazole (3.57 g, 10 mmol), indium powder (8.03 g, 70 mmol), ethanol (40 mL), and sat. aqueous ammonium chloride (12 mL), added in that order, was stirred under reflux for 2 h. 2 M NaOH (50 mL) was added and the mixture was filtered over Celite. The reaction flask and Celite pad were washed with methylene chloride (50 mL). The combined filtrates were evaporated to remove dichloromethane and most ethanol. The precipitate was collected by filtration, washed with water (15 mL) and ethanol (3 mL), and air-dried to give the desired product (yellow to orange solid, 75–80% yield).

¹H NMR (CDCl₃) δ 7.79 (d, 2H, J=8.4 Hz), 7.22~7.26 (m, 2H), 6.92 (t, 1H, J=7.3 Hz), 6.87 (d, 2H, J=8.1 Hz), 6.69 (d, 2H, J=8.8 Hz), 4.17 (t, 2H, J=6.2 Hz), 3.99 (s, 2H), 3.02 (t, 2H, J=6.2 Hz). MS (ES+) m/e 328 (M+1).

c) 2-{{(2-Phenoxyethyl)thio}methyl}-5-{4-[{(4-(N,N-dimethylamino)butanoyl)amino]phenyl}}-1,3,4-oxadiazole

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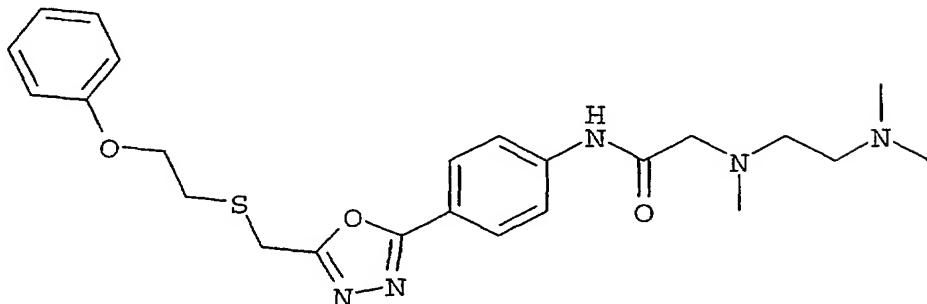


To a suspension of 4-(N,N-dimethylamino)butyric acid hydrochloride (1.67 g, 10 mmol) in N,N-dimethylformamide (0.5 mL) and methylene chloride (50 mL) was added oxalyl chloride (1.48 mL, 17 mmol) dropwise over a period of 10 min. The mixture was stirred at room temperature for 2 h and evaporated under reduced pressure to remove methylene chloride and excess oxalyl chloride. The resultant white solid was dissolved in methylene chloride (5 mL) and added dropwise over 2 min to a solution of 2-{{[(2-phenoxyethyl)thio]methyl}-5-(4-aminophenyl)-1,3,4-oxadiazole (982 mg, 3 mmol), 4-(N,N-dimethylamino)pyridine (183 mg, 1.5 mmol), and triethylamine (1.01 g, 10 mmol) in methylene chloride (25 mL) at 0 °C. After 20 min the cooling bath was removed, and the mixture was allowed to stir overnight, washed with 2 M NaOH (4 x 15 mL), dried (MgSO₄), and concentrated. The residue was dissolved in methanol (30 mL), diluted with water (5 mL), and concentrated under reduced pressure to remove most methanol. The precipitate was collected by filtration, washed with water (5 mL), redissolved in methylene chloride (30 mL), washed with water (15 mL), dried (MgSO₄), and concentrated. The residue was triturated from methylene chloride and hexanes to give an off-white solid (839 mg, 64%).

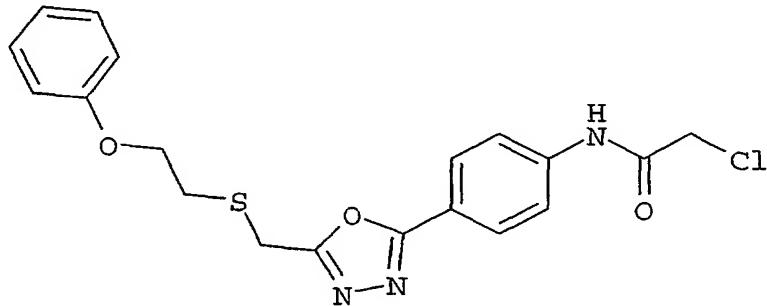
¹H NMR (CDCl₃) δ 10.60 (s, 1H), 7.94 (d, 2H, J=8.4 Hz), 7.65 (d, 2H, J=8.8 Hz), 7.22~7.26 (m, 2H), 6.92 (t, 1H, J=7.3 Hz), 6.87 (d, 2H, J=7.7 Hz), 4.18 (t, 2H, J=6.2 Hz), 4.02 (s, 2H), 3.03 (t, 2H, J=6.0 Hz), 2.49~2.57 (m, 4H), 2.36 (s, 6H), 1.87~1.91 (m, 2H). IR (KBr, cm⁻¹) 3494, 3456, 3313, 2939, 1666, 1605, 1499, 1465, 1243, 1177, 1035, 760. MS (ES+) m/e 441 (M+1). Anal. Calcd for C₂₃H₂₈N₄O₃S: C, 62.70; H, 6.41; N, 12.72; S, 7.28. Found C, 62.59; H, 6.51; N, 12.69; S, 7.23.

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Preparation of 2-{{(2-Phenoxyethyl)thio]methyl}-5-{4-[2-(N,N',N'-trimethylethylenediamino)acetamido]phenyl}-1,3,4-oxadiazole



- a) 2-{{(2-Phenoxyethyl)thio]methyl}-5-[4-(2-chloroacetamido)phenyl]-1,3,4-
5 oxadiazole



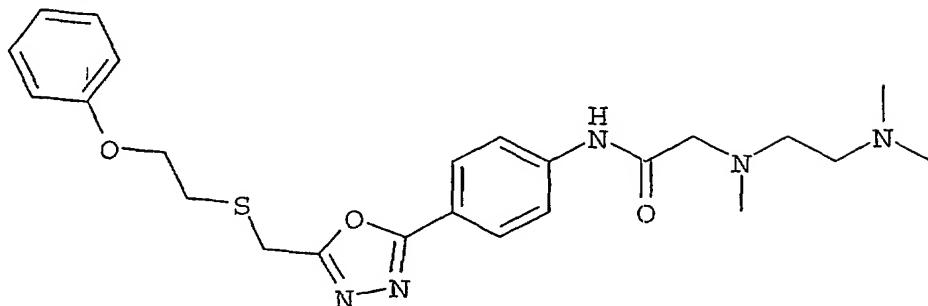
A suspension of 2-{{(2-phenoxyethyl)thio]methyl}-5-(4-aminophenyl)-1,3,4-oxadiazole (1.636 g, 5 mmol) in toluene (30 mL) was heated to approximately 50 °C and chloroacetic chloride (1.6 mL, 20 mmol) was added. The mixture was stirred under reflux
10 for 4 h and allowed to cool to room temperature. The solid was collected by filtration, washed with hexanes and air-dried to give the desired product (1.61 g, 80%).

¹H NMR (CDCl₃) δ 8.8 (s, 1H), 8.01 (d, 2H, J=8.6 Hz), 7.70 (d, 2H, J=8.6 Hz), 7.23~7.27 (m, 2H), 6.93 (t, 1H, J=7.4 Hz), 6.87 (d, 2H, J=7.8 Hz), 4.21 (s, 2H), 4.19 (t, 2H, J=6.2 Hz), 4.03 (s, 2H), 3.04 (t, 2H, J=6.2 Hz). MS (ES+) m/e 404 (M+1).

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- b) 2-{{(2-Phenoxyethyl)thio]methyl}-5-{4-[2-(N,N',N'-trimethylethylenediamino)acetamido]phenyl}-1,3,4-oxadiazole



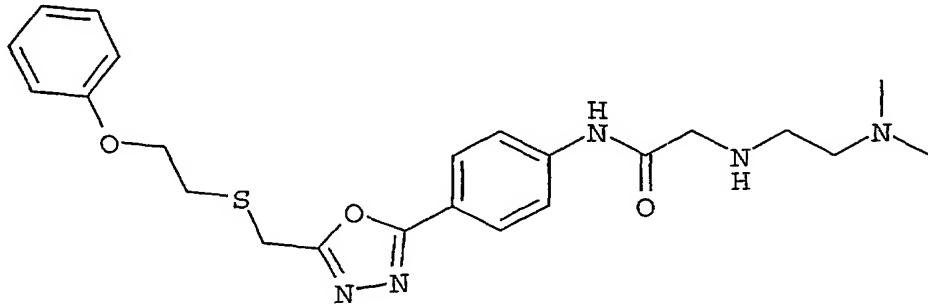
A mixture of 2-{{(2-phenoxyethyl)thio]methyl}-5-[4-(2-chloroacetamido)phenyl]-
 5 1,3,4-oxadiazole (100 mg, 0.25 mmol) and N,N,N'-trimethylethylenediamine (1.5 mL)
 was stirred at room temperature overnight and excess N,N,N'-trimethylethylenediamine
 was evaporated under vacuum. The residue was purified by preparative TLC (silica gel,
 10% methanol/methylene chloride) to give a pale yellow oil (100 mg, 85%).

¹H NMR (CDCl₃) δ 10.41 (s, 1H), 7.96 (d, 2H, J=8.5 Hz), 7.79 (m, 2H),
 10 7.23~7.27 (m, 2H), 6.93 (t, 1H, J=7.3 Hz), 6.88 (d, 2H, J=7.6 Hz), 4.19 (t, 2H, J=6.0 Hz),
 4.02 (s, 2H), 3.20 (s, 2H), 3.03 (t, 2H, J=6.0 Hz), 2.60 (m, 2H), 2.44 (s, 6H), 2.27 (m,
 5H). IR (film, cm⁻¹) 3458, 3321, 2940, 1669, 1602, 1501, 1411, 1257, 1181, 753. MS
 (ES+) m/e 468 (M+1). Anal. Calcd for C₂₅H₃₃N₅O₂S: C, 64.21; H, 7.11; N, 14.98; S,
 6.86. Found C, 64.10; H, 7.06; N, 14.79; S, 6.88.

15

Example 151

Preparation of 2-{{(2-Phenoxyethyl)thio]methyl}-5-{4-[2-(N',N'-dimethylethylenediamino)acetamido]phenyl}-1,3,4-oxadiazole



20 A mixture of 2-{{(2-phenoxyethyl)thio]methyl}-5-[4-(2-chloroacetamido)phenyl]-
 1,3,4-oxadiazole (50 mg, 0.12 mmol) and N,N-dimethylethylenediamine (1 mL) was

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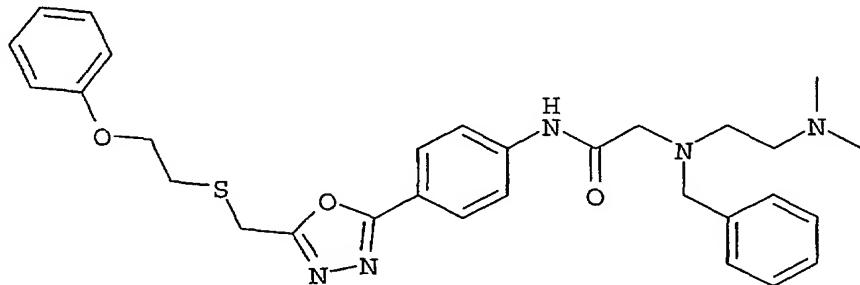
stirred at room temperature overnight and excess N,N-dimethylethylenediamine was evaporated under vacuum. The residue was purified by preparative TLC (silica gel, 10% methanol/methylene chloride) to give a pale yellow oil (28 mg, 51%).

¹H NMR (CDCl₃) δ 7.96 (d, 2H, J=8.7 Hz), 7.79 (d, 2H, J=8.8 Hz), 7.22~7.26 (m, 5 2H), 6.92 (t, 1H, J=7.7 Hz), 6.87 (d, 2H, J=7.7 Hz), 4.18 (t, 2H, J=6.2 Hz), 4.02 (s, 2H), 3.41 (s, 2H), 3.04 (s, 1H), 3.03 (t, 2H, J=5.9 Hz), 2.79 (t, 2H, J=5.6 Hz), 2.50 (t, 2H, J=5.6 Hz), 2.31 (s, 6H). IR (film, cm⁻¹) 3464, 3327, 2959, 1669, 1604, 1521, 1260, 1134, 757. MS (ES+) m/e 454 (M+1). Anal. Calcd for C₂₄H₃₁N₅O₂S: C, 63.55; H, 6.89; N, 15.44; S, 7.07. Found C, 63.75; H, 6.91; N, 15.28; S, 7.26.

10

Example 152

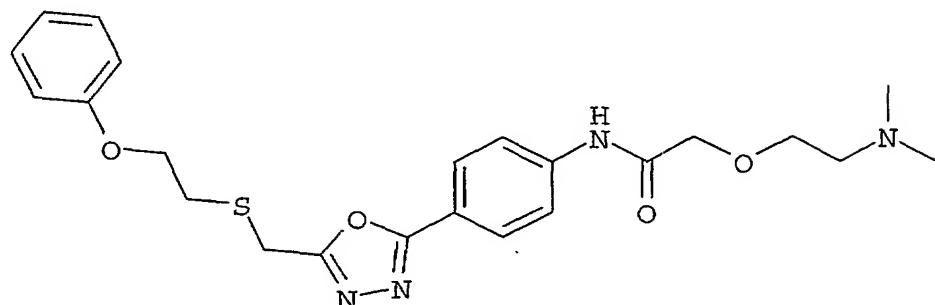
Preparation of 2-{{(2-Phenoxyethyl)thio}methyl}-5-{4-[2-(N-benzyl-N',N'-dimethylethylenediamino)acetamido]phenyl}-1,3,4-oxadiazole



¹H NMR (CDCl₃) δ 10.75 (s, 1H), 7.96 (d, 2H, J=8.4 Hz), 7.72 (d, 2H, J=8.3 Hz), 7.24~7.31 (m, 7H), 6.93 (t, 1H, J=7.5 Hz), 6.88 (d, 2H, J=8.0 Hz), 4.19 (t, 2H, J=6.0 Hz), 4.03 (s, 2H), 3.75 (s, 2H), 3.28 (s, 2H), 3.04 (t, 2H, J=6.0 Hz), 2.70 (t, 2H, J=5.4 Hz), 2.33~2.42 (m, 2H), 2.17 (s, 6H). IR (film, cm⁻¹) 3455, 3330, 2946, 1670, 1606, 1500, 25 1420, 1301, 1256, 1177, 758. MS (ES+) m/e 544 (M+1). Anal. Calcd for C₃₁H₃₇N₅O₂S: C, 68.48; H, 6.86; N, 12.88; S, 5.90. Found C, 68.53; H, 6.63; N, 12.71; S, 5.82.

Example 153

Preparation of 2-{{(2-Phenoxyethyl)thio]methyl}-5-{4-[2-((2-(N,N-dimethylamino)ethoxy)acetamido)phenyl]-1,3,4-oxadiazole

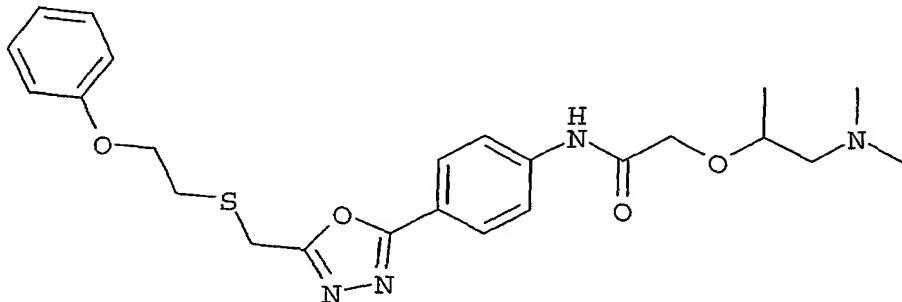


5 Sodium hydride (60% suspension in oil, 64 mg, 1.6 mmol) was washed with tetrahydrofuran (10 mL), suspended in N,N-dimethylformamide (15 mL) and cooled to 0 °C. N,N-dimethylethanamine (171 mg, 1.92 mmol) was added dropwise over 2 min with stirring, and the mixture was allowed-to-warm-to-room-temperature-and-stir-for-30 min. 2-{{(2-Phenoxyethyl)thio]methyl}-5-[4-(2-chloroacetamido)phenyl]-1,3,4-oxadiazole (130 mg, 0.32 mmol) was added and stirring was continued for 18 h. The reaction mixture was poured into water (40 mL) and extracted with ethyl acetate (4 x 15 mL). The combined ethyl acetate extracts were washed with water (2 x 15 mL) and brine (20 mL), dried (MgSO_4), and concentrated. The residue was purified by chromatography (silica gel, 10% methanol/methylene chloride) to give a colorless oil (77 mg, 53%).

10 ^1H NMR (CDCl_3) δ 10.25 (s, 1H), 7.97 (d, 2H, $J=8.8$ Hz), 7.78 (d, 2H, $J=8.4$ Hz), 7.22~7.27 (m, 7H), 6.93 (t, 1H, $J=7.3$ Hz), 6.87 (d, 2H, $J=7.6$ Hz), 4.19 (t, 2H, $J=6.2$ Hz), 4.11 (s, 2H), 4.02 (s, 2H), 3.69 (t, 2H, $J=5.0$ Hz), 3.03 (t, 2H, $J=6.0$ Hz), 2.60 (m, 2H), 2.36 (s, 6H). IR (film, cm^{-1}) 3470, 3334, 2934, 1669, 1599, 1498, 1412, 1248, 1182, 1036, 756. MS (ES+) m/e 457 (M+1). Anal. Calcd for $\text{C}_{23}\text{H}_{28}\text{N}_4\text{O}_4\text{S}$: C, 60.51; H, 6.18; N, 12.27; S, 7.02. Found C, 60.37; H, 6.10; N, 12.17; S, 6.94.

Example 154

Preparation of (+)-2-{{(2-phenoxyethyl)thio]methyl}-5-{4-[2-(2-(N,N-dimethylamino)-1-methylethoxy)acetamido]phenyl}-1,3,4-oxadiazole

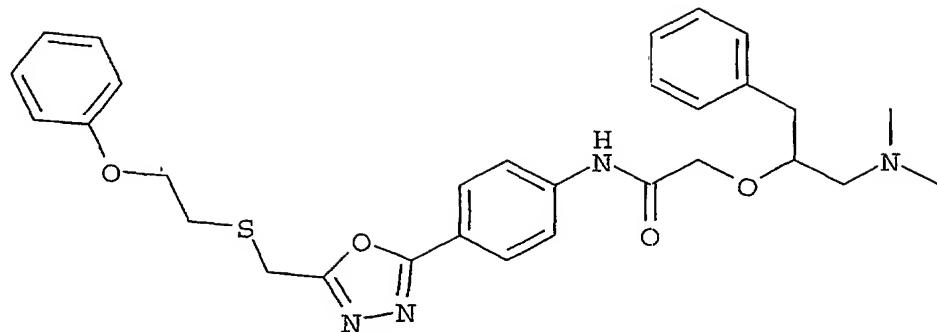


- 5 Sodium hydride (60% suspension in oil, 200 mg, 5 mmol) was washed with tetrahydrofuran (10 mL), suspended in N,N-dimethylformamide (5 mL) and cooled to 0 °C with stirring. 1-(N,N-dimethylamino)-2-propanol (1.03 g, 10 mmol) in N,N-dimethylformamide (2 mL) was added dropwise, and stirring was continued for 10 min at 0 oC and 30 min at room temperature. 2-{{(2-Phenoxyethyl)thio]methyl}-5-[4-(2-chloroacetamido)phenyl]-1,3,4-oxadiazole (202 mg, 0.5 mmol) was added and the resultant mixture was stirred at room temperature for 2.5 h. The reaction mixture was diluted with ethyl acetate (40 mL), washed with water (5 x 15 mL) and brine (15 mL), dried (MgSO_4), and concentrated. The residue was purified by chromatography (silica gel, 5% methanol/methylene chloride) to give a colorless oil (120 mg, 51%).
- 10 ^1H NMR (CDCl_3) δ 10.83 (s, 1H), 7.97 (d, 2H, $J=8.8$ Hz), 7.73 (d, 2H, $J=8.5$ Hz), 7.22~7.26 (m, 2H), 6.93 (t, 1H, $J=7.7$ Hz), 6.87 (d, 2H, $J=7.6$ Hz), 4.23 (d, 1H, $J=16.9$ Hz), 4.19 (t, 2H, $J=6.2$ Hz), 4.03 (s, 2H), 3.95 (d, 1H, $J=16.9$ Hz), 3.55 (m, 1H), 3.03 (t, 2H, $J=6.2$ Hz), 2.61 (t, 1H, $J=11.5$ Hz), 2.31 (s, 6H), 2.15 (m, 1H), 1.13 (d, 3H, $J=5.8$ Hz). IR (film, cm^{-1}) 3456, 3344, 2931, 1668, 1602, 1503, 1412, 1248, 1172, 1037, 756.
- 15 MS (ES+) m/e 471 (M+1). Anal. Calcd for $\text{C}_{24}\text{H}_{30}\text{N}_4\text{O}_4\text{S}$: C, 61.26; H, 6.43; N, 11.91; S, 6.81. Found C, 61.23; H, 6.27; N, 11.79; S, 6.88.

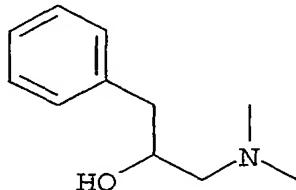
Example 155

- Preparation of (+)-2-{{(2-phenoxyethyl)thio]methyl}-5-{4-[2-(1-benzyl-2-(N,N-dimethylamino)ethoxy)acetamido]phenyl}-1,3,4-oxadiazole

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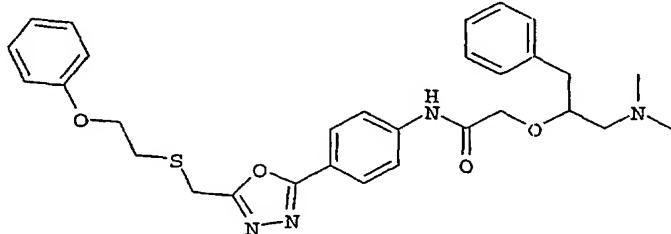
a) (+)-1-Benzyl-2-(N,N-dimethylamino)ethanol



To a solution of 2,3-epoxypropylbenzene (1.34 g, 10 mmol) and lithium perchlorate (1.17 g, 11 mmol) in acetonitrile (10 mL) was added 2 M dimethylamine in tetrahydrofuran (5 mL 10 mmol). The resultant mixture was stirred at room temperature overnight, diluted with ether (20 mL), washed with water (3 x 10 mL), dried (MgSO₄), and concentrated to give a yellow oil (1.61 g, 90%). This material was used in the next step without further purification.

¹H NMR (CDCl₃) δ 7.16-7.28 (m, 5H), 3.84 (m, 1H), 2.78 (dd, 1H, J=13.5, 7.1 Hz), 2.63 (dd, 1H, J=13.5, 5.6 Hz), 2.30 (dd, 1H, J=11.8, 10.4 Hz), 2.22 (s, 6H), 2.15 (dd, 1H, J=12.1, 3.3 Hz). MS (ES+) m/e 181 (M+1).

b) (+)-2-{[(2-Phenoxyethyl)thio]methyl}-5-{4-[2-(1-benzyl-2-(N,N-dimethylamino)ethoxy)acetamido]phenyl}-1,3,4-oxadiazole



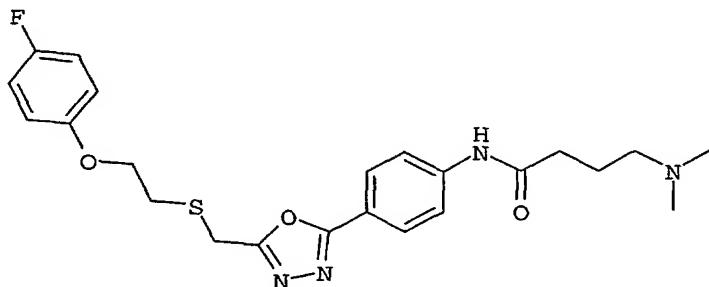
Sodium hydride (60% suspension in oil, 80 mg, 2 mmol) was washed with tetrahydrofuran (10 mL), suspended in N,N-dimethylformamide (4 mL) and cooled to 0

^oC with stirring. (+)-1-benzyl-2-(N,N-dimethylamino)ethanol (358 mg, 2 mmol) in N,N-dimethylformamide (3 mL) was added dropwise, and stirring was continued for 10 min at 0 oC and 20 min at room temperature. 2-{{[(2-Phenoxyethyl)thio]methyl}-5-[4-(2-chloroacetamido)phenyl]-1,3,4-oxadiazole (202 mg, 0.5 mmol), followed by sodium iodide (149 mg, 1 mmol) was added and the resultant mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with ethyl acetate (50 mL), washed with water (4 x 25 mL) and brine (25 mL), dried (MgSO_4), and concentrated. The residue was purified by chromatography (silica gel, 5% methanol/methylene chloride) to give a colorless oil (114 mg, 42%).

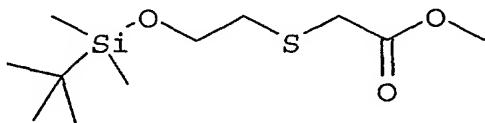
¹H NMR (CDCl_3) δ 10.87 (s, 1H), 7.98 (d, 2H, $J=8.8$ Hz), 7.67 (d, 2H, $J=8.8$ Hz), 7.17~7.32 (m, 7H), 6.92 (t, 1H, $J=7.3$ Hz), 6.87 (d, 2H, $J=8.0$ Hz), 4.18 (t, 2H, $J=6.2$ Hz), 4.11 (d, 1H, $J=17.2$ Hz), 4.02 (s, 2H), 3.75 (d, 1H, $J=17.2$ Hz), 3.66 (m, 1H), 3.03 (t, 2H, $J=6.2$ Hz), 2.76 (m, 2H), 2.62 (dd, 1H, $J=13.0, 10.4$ Hz), 2.28 (m, 1H), 2.27 (s, 6H). IR (film, cm^{-1}) 3460, 3334, 2934, 1658, 1600, 1501, 1426, 1280, 1175, 1053, 761. MS (ES+) m/e 547 (M+1). Anal. Calcd for $\text{C}_{30}\text{H}_{34}\text{N}_4\text{O}_4\text{S}$: C, 65.91; H, 6.27; N, 10.25; S, 5.87. Found C, 66.04; H, 6.25; N, 10.31; S, 5.49.

Example 156

Preparation of 2-{{[(2-(4-Fluorophenoxy)ethyl)thio]methyl}-5-[4-[(4-(N,N-dimethylamino)butanoyl)amino]phenyl]-1,3,4-oxadiazole



a) Methyl 2-{{[2-(tert-butyldimethylsilyloxy)ethyl]thio}acetate



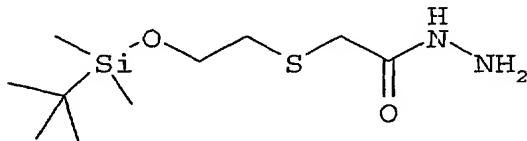
A mixture of methyl thioglycolate (4.78 g, 45 mmol), 2-bromoethoxy-tert-butylidemethylsilane (7.18 g, 30 mmol), and potassium carbonate (10.37 g, 75 mmol) in

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tetrahydrofuran (150 mL) was stirred under reflux overnight. The resultant mixture was cooled to room temperature, diluted with ether (100 mL), washed with water (3 x 100 mL) and brine (100 mL), dried (MgSO_4), and concentrated to give a colorless oil (7.85 g, 99%).

5 ^1H NMR (CDCl_3) δ 3.78 (t, 2H, $J=6.6$ Hz), 3.71 (s, 3H), 3.27 (s, 2H), 2.74 (t, 2H, $J=6.6$ Hz), 0.87 (s, 9H), 0.04 (s, 6H). MS (ES+) m/e 265 (M+1).

b) 2-{[2-(tert-butyldimethylsilyloxy)ethyl]thio}acetic hydrazide

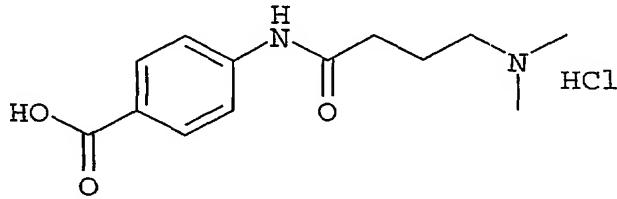


10

A mixture of methyl 2-{[2-(tert-butyldimethylsilyloxy)ethyl]thio}acetate (2.65 g, 10 mmol) and hydrazine monohydrate (5 g, 100 mmol) in ethanol was stirred at room temperature for 2 h and concentrated. The residue was taken up in ethyl acetate (50 mL), washed with water (5 x 20 mL), dried (MgSO_4), and concentrated to give a colorless oil (2.53 g, 96%).

15 ^1H NMR (CDCl_3) δ 7.99 (br s, 1H), 3.85 (br s, 2H), 3.79 (t, 2H, $J=6.0$ Hz), 3.29 (s, 2H), 2.68 (t, 2H, $J=6.2$ Hz), 0.88 (s, 9H), 0.06 (s, 6H). MS (ES+) m/e 265 (M+1).

c) 4-{[4-(N,N-Dimethylamino)butanoyl]amino}benzoic acid hydrochloride



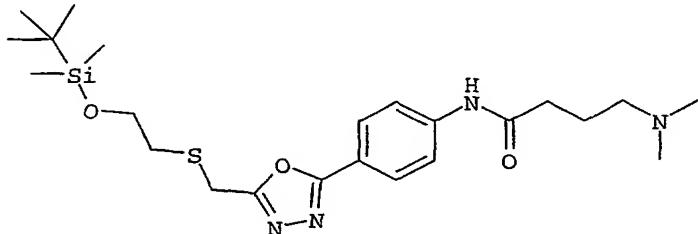
20

A mixture of methyl 4-aminobenzoate (4.53 g, 30 mmol), 4-(N,N-dimethylamino)butyric acid hydrochloride (6.71 g, 40 mmol), diisopropylcarbodiimide (5.05 g, 40 mmol), and 1-hydroxybenzotriazole (5.41 g, 40 mmol) in N,N-dimethylformamide (200 mL) was stirred at room temperature over the weekend. The reaction mixture was poured into water (600 mL), made basic with 2 M NaOH to pH ~10, and extracted with ethyl acetate (5 x 150 mL). The combined ethyl acetate extracts were

washed with 2 M NaOH (2 x 150 mL), dried (MgSO_4), and concentrated. The residue was purified on a cation exchange column (Bio-Rad 50W-X2 resin) to give colorless oil (6.18 g, 78%). This material (5.28 g, 20 mmol) was dissolved in tetrahydrofuran (30 mL) and stirred with 2 M NaOH (50 mL, 100 mmol) at room temperature overnight. Ether (30 mL) was added and the phases were separated. The aqueous layer was loaded to an anion exchange column (Bio-Rad AG1-X2 resin). The column was eluted with water until the eluent became neutral, followed by 4 M HCl in dioxane to recover the product. Dioxane was evaporated. The resultant solid was washed with dioxane (250 mL) and methylene chloride (200 mL) to give the final product (3.68, 64%).

¹⁰ ^1H NMR (DMSO-d₆) δ 10.40 (s, 1H), 10.0 (br s, 1H), 7.84 (d, 2H, $J=8.8$ Hz), 7.68 (d, 2H, $J=8.8$ Hz), 3.03 (m, 2H), 2.72 (s, 6H), 2.45 (m, 2H), 1.92 (m, 2H). MS (ES-) m/e 249 (M-1).

¹⁵ d) 2-{{[2-(tert-Butyldimethylsilyloxy)ethyl]thio}methyl}-5-{4-[(N,N-dimethylamino)butanoyl]amino}phenyl]-1,3,4-oxadiazole



To a stirred mixture of 2-{{[2-(tert-butyldimethylsilyloxy)ethyl]thio}acetic hydrazide (2.65 g, 10 mmol), 4-{{[4-(N,N-Dimethylamino)butanoyl]amino}benzoic acid hydrochloride (2.86 g, 10 mmol), and 4-(N,N-dimethylaminophenyl)diphenylphosphine (9.16 g, 30 mmol) in acetonitrile (100 mL) at 0 °C was added slowly a solution of triethylamine (6.07 g, 60 mmol) in carbon tetrachloride (7.69 g, 50 mmol). The resultant mixture was stirred at room temperature overnight and concentrated. The residue was taken up in methylene chloride (150 mL), washed with 2 M NaOH (2 x 50 mL), dried (MgSO_4), and concentrated. The residue was purified by chromatography (silica gel, 10% methanol/methylene chloride to 5% methanol and 5% 7 M methanolic ammonia/methylene chloride) to give a pale yellow oil (1.79 g, 38%).

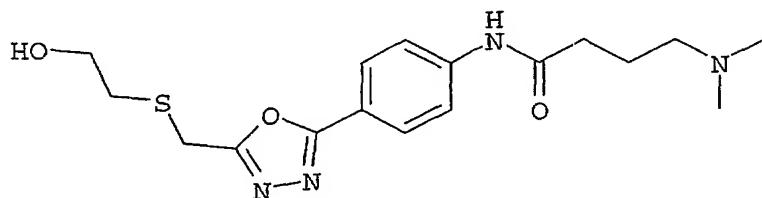
^1H NMR (CDCl_3) δ 10.16 (s, 1H), 7.97 (d, 2H, $J=8.8$ Hz), 7.87 (d, 2H, $J=8.8$ Hz), 3.96 (s, 2H), 3.81 (t, 2H, $J=6.4$ Hz), 3.0 (t, 2H, $J=5.6$ Hz), 2.75~2.85 (m, 4H), 2.76 (s,

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6H), 2.15~2.19 (m, 2H), 0.87 (s, 9H), 0.05 (s, 6H). IR (film, cm^{-1}) 3473, 3327, 2963, 1659, 1598, 1496, 1245, 1181, 1088, 750. MS (ES+) m/e 479 (M+1). Anal. Calcd for $\text{C}_{23}\text{H}_{38}\text{N}_4\text{O}_3\text{SSi}$: C, 57.71; H, 8.00; N, 11.70; S, 6.70. Found C, 57.57; H, 8.12; N, 11.52; S, 6.91.

5

e) 2-{{[(2-hydroxyethyl)thio]methyl}-5-{4-[(N,N-dimethylamino)butanoyl]amino]phenyl}-1,3,4-oxadiazole

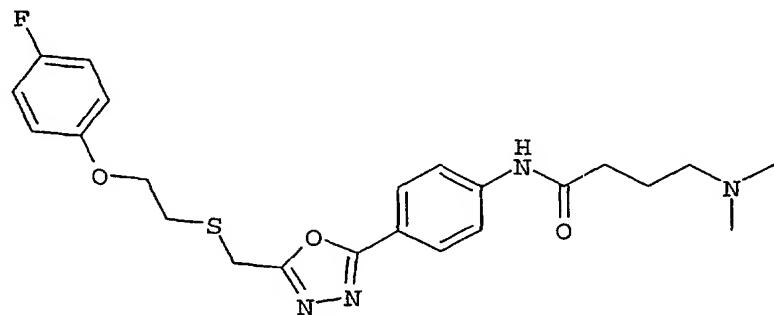


2-{{[(2-(tert-Butyldimethylsilyloxy)ethyl)thio]methyl}-5-{4-[(N,N-dimethylamino)butanoyl]amino]phenyl}-1,3,4-oxadiazole (1.47 g, 3 mmol) was stirred in 10 2 M HCl (15 mL) until it appeared completely dissolved (~30 min). The solution was washed with methylene chloride (3 x 10 mL), treated with 2 M NaOH to pH ~11, and extracted with methylene chloride (3 x 10 mL). The combined methylene chloride extracts were dried (MgSO_4) and concentrated to give a pale yellow solid (430 mg, 39%).

15 ^1H NMR (CDCl_3) δ 10.66 (s, 1H), 7.96 (d, 2H, $J=7.8$ Hz), 7.66 (d, 2H, $J=7.8$ Hz), 3.94 (s, 2H), 3.81 (t, 2H, $J=5.9$ Hz), 2.83 (t, 2H, $J=5.6$ Hz), 2.49~2.56 (m, 4H), 2.36 (s, 6H), 1.88 (m, 2H). IR (KBr, cm^{-1}) 3482, 3330, 2957, 1661, 1603, 1501, 1411, 1168, 756. MS (ES+) m/e 365 (M+1). Anal. Calcd for $\text{C}_{17}\text{H}_{24}\text{N}_4\text{O}_3\text{S}$: C, 56.02; H, 6.64; N, 15.37; S, 8.80. Found C, 56.16; H, 6.74; N, 15.38; S, 8.94.

20

f) 2-{{[(2-(4-Fluorophenoxy)ethyl)thio]methyl}-5-{4-[(N,N-dimethylamino)butanoyl]amino]phenyl}-1,3,4-oxadiazole



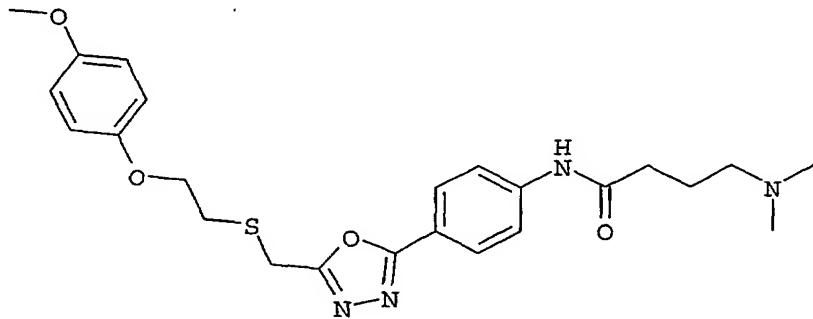
-315-

A solution of 2-{{(2-hydroxyethyl)thio}methyl}-5-{4-[(N,N-dimethylamino)butanoyl]amino}phenyl]-1,3,4-oxadiazole (130 mg, 0.36 mmol), 4-fluorophenol (161 mg, 1.44 mmol), and triphenylphosphine (184 mg, 0.7 mmol) in tetrahydrofuran (6 mL) was cooled with an ice bath and diisopropyl azodicarboxylate (142 mg, 0.7 mmol) in tetrahydrofuran (1 mL) was added dropwise. After 5 min the cooling bath was removed and the mixture was stirred at room temperature overnight. The resultant mixture was diluted with ethyl acetate (10 mL), washed with 2 M NaOH (3 x 10 mL), dried (MgSO_4), and concentrated. The residue was purified by preparative TLC (silica gel, 5% methanol and 5% 7 M methanolic ammonia in methylene chloride, twice developed) to give a colorless oil (151 mg, 92%).

^1H NMR (CDCl_3) δ 10.67 (s, 1H), 7.94 (d, 2H, $J=8.8$ Hz), 7.65 (d, 2H, $J=8.4$ Hz), 6.92 (t, 2H, $J=8.6$ Hz), 6.79~6.82 (m, 2H), 4.13 (t, 2H, $J=6.2$ Hz), 4.01 (s, 2H), 3.01 (t, 2H, $J=6.2$ Hz), 2.54 (t, 2H, $J=6.4$ Hz), 2.49 (t, 2H, $J=5.8$ Hz), 2.35 (s, 6H), 1.84~1.88 (m, 2H). IR (film, cm^{-1}) 3456, 3322, 2957, 1657, 1600, 1446, 1382, 1215, 1177, 755. MS (ES+) m/e 459 (M+1). Anal. Calcd for $\text{C}_{23}\text{H}_{27}\text{FN}_4\text{O}_3\text{S}$: C, 60.24; H, 5.93; N, 12.22; S, 6.99. Found C, 60.13; H, 5.86; N, 12.36; S, 6.94.

Example 157

Preparation of 2-{{(2-(4-Methoxyphenoxy)ethyl)thio}methyl}-5-{4-[(N,N-dimethylamino)butanoyl]amino}phenyl]-1,3,4-oxadiazole



A solution of 2-{{(2-hydroxyethyl)thio}methyl}-5-{4-[(N,N-dimethylamino)butanoyl]amino}phenyl]-1,3,4-oxadiazole (80 mg, 0.22 mmol), 4-methoxyphenol (109 mg, 0.88 mmol), and triphenylphosphine (115 mg, 0.44 mmol) in tetrahydrofuran (8 mL) was cooled with an ice bath and diisopropyl azodicarboxylate (89 mg, 0.44 mmol) in tetrahydrofuran (0.5 mL) was added dropwise. After 5 minutes the

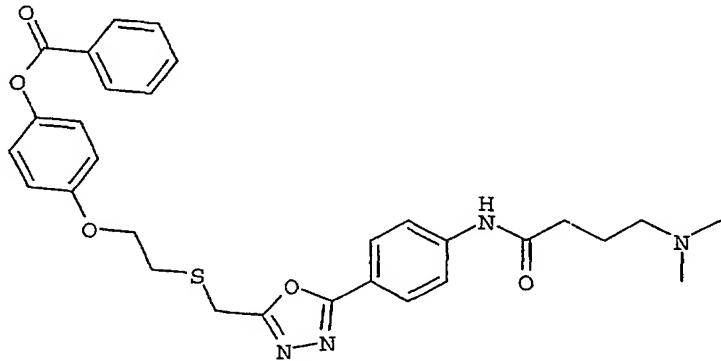
-316-

cooling bath was removed and the mixture was stirred at room temperature overnight. The resultant mixture was diluted with ethyl acetate (10 mL), washed with 2 M NaOH (3 x 5 mL), dried (MgSO_4), and concentrated. The residue was purified by preparative TLC (silica gel, 5% methanol and 5% 7 M methanolic ammonia in methylene chloride, twice developed) to give a colorless oil (53 mg, 50%).

¹H NMR (CDCl_3) δ 10.63 (s, 1H), 7.94 (d, 2H, $J=8.8$ Hz), 7.66 (d, 2H, $J=8.7$ Hz), 6.81 (d, 2H, $J=9.5$ Hz), 6.78 (d, 2H, $J=9.2$ Hz), 4.13 (t, 2H, $J=6.2$ Hz), 4.01 (s, 2H), 3.73 (s, 3H), 3.0 (t, 2H, $J=6.2$ Hz), 2.49~2.57 (m, 4H), 2.36 (s, 6H), 1.83~1.91 (m, 2H). IR (film, cm^{-1}) 3470, 3341, 2955, 1661, 1606, 1500, 1438, 1388, 1237, 1176, 764. MS (ES+) m/e 471 (M+1). Anal. Calcd for $\text{C}_{24}\text{H}_{30}\text{N}_4\text{O}_4\text{S}$: C, 61.26; H, 6.43; N, 11.91; S, 6.81. Found C, 61.29; H, 6.45; N, 11.74; S, 6.73.

Example 158

Preparation of 2-{{[(2-(4-Benzoyloxyphenoxy)ethyl)thio]methyl}-5-{4-[¹⁵(N,N-dimethylamino)butanoyl]amino}phenyl}-1,3,4-oxadiazole



A solution of 2-{{[(2-hydroxyethyl)thio]methyl}-5-{4-[²⁰(N,N-dimethylamino)butanoyl]amino}phenyl}-1,3,4-oxadiazole (80 mg, 0.22 mmol), 4-hydroxyphenyl benzoate (189 mg, 0.88 mmol), and triphenylphosphine (116 mg, 0.44 mmol) in tetrahydrofuran (8 mL) was cooled with an ice bath and diisopropyl azodicarboxylate (89 mg, 0.44 mmol) in tetrahydrofuran (0.5 mL) was added dropwise. After 5 min the cooling bath was removed and the mixture was stirred at room temperature overnight. The resultant mixture was diluted with ethyl acetate (10 mL), washed with 2 M NaOH (3 x 5 mL), dried (MgSO_4), and concentrated. The residue was

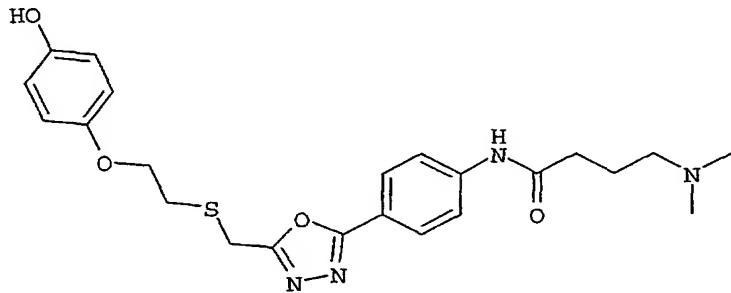
purified by preparative TLC (silica gel, 5% methanol and 5% 7 M methanolic ammonia in methylene chloride, twice developed) to give colorless oil (72 mg, 58%).

¹H NMR (CDCl₃) δ 10.55 (s, 1H), 8.17 (d, 2H, J=7.7 Hz), 7.95 (d, 2H, J=8.4 Hz), 7.67 (d, 2H, J=8.4 Hz), 7.61 (t, 1H, J=7.3 Hz), 7.48 (t, 2H, J=7.6 Hz), 7.09 (d, 2H, J=9.2 Hz), 6.91 (d, 2H, J=8.8 Hz), 4.19 (t, 2H, J=6.0 Hz), 4.02 (s, 2H), 3.05 (t, 2H, J=6.2 Hz), 2.46~2.57 (m, 4H), 2.37 (s, 6H), 1.86~1.90 (m, 2H). IR (film, cm⁻¹) 3420, 3035, 2957, 2771, 1763, 1660, 1601, 1499, 1423, 1215, 1170, 755. MS (ES+) m/e 561 (M+1). Anal. Calcd for C₃₀H₃₂N₄O₅S: C, 64.27; H, 5.75; N, 9.99; S, 5.72. Found C, 64.40; H, 5.62; N, 10.03; S, 5.74.

10

Example 159

Preparation of 2-{{[(2-(4-Hydroxyphenoxy)ethyl)thio]methyl}-5-{4-[(N,N-dimethylamino)butanoyl]amino}phenyl}-1,3,4-oxadiazole

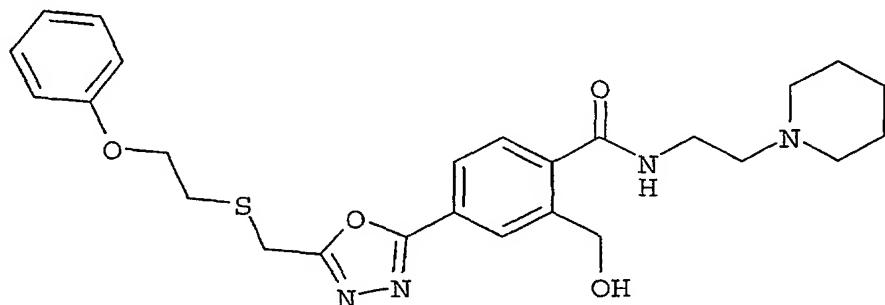


15 To a solution of 2-{{[(2-(4-benzoyloxyphenoxy)ethyl)thio]methyl}-5-{4-[(N,N-dimethylamino)butanoyl]amino}phenyl}-1,3,4-oxadiazole (50 mg, 0.1 mmol) in MeOH (1 mL) and tetrahydrofuran (0.5 mL) was added 2M NaOH (1 mL, 2 mmol). The mixture was stirred at room temperature overnight and extracted with methylene chloride (3 x 5 mL). The combined methylene chloride extracts were washed with water (1 mL), dried (MgSO₄), and concentrated to give a colorless oil (30 mg, 66%).

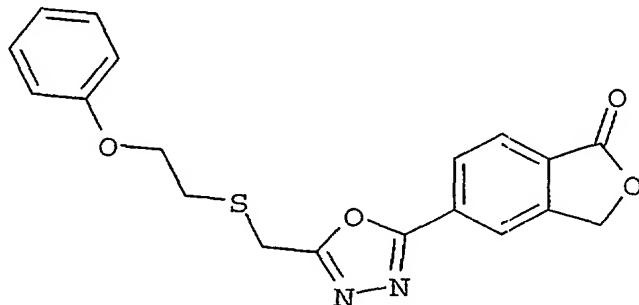
20 ¹H NMR (CDCl₃) δ 10.60 (s, 1H), 7.86 (d, 2H, J=8.4 Hz), 7.58 (d, 2H, J=8.4 Hz), 6.72 (d, 2H, J=8.8 Hz), 6.67 (d, 1H, J=9.2 Hz), 4.07 (t, 2H, J=6.2 Hz), 4.0 (s, 2H), 3.01 (t, 2H, J=6.2 Hz), 2.44~2.56 (m, 4H), 2.34 (s, 6H), 1.83~1.92 (m, 2H). IR (film, cm⁻¹) 3458, 3333, 2965, 1660, 1597, 1500, 1410, 1395, 1264, 1163, 757. MS (ES+) m/e 457 (M+1).
25 Anal. Calcd for C₂₃H₂₈N₄O₄S: C, 60.51; H, 6.18; N, 12.27; S, 7.02. Found C, 61.02; H, 6.26; N, 12.09; S, 7.08.

Example 160

Preparation of 2-{{(2-Phenoxyethyl)thio}methyl}-5-{3-hydroxymethyl-4-[(2-piperidinoethyl)amino]carbonyl}phenyl}-1,3,4-oxadiazole



- 5 a) 5-{2-[(2-Phenoxyethyl)thio)methyl]-1,3,4-oxadiazol-5-yl}phthalide

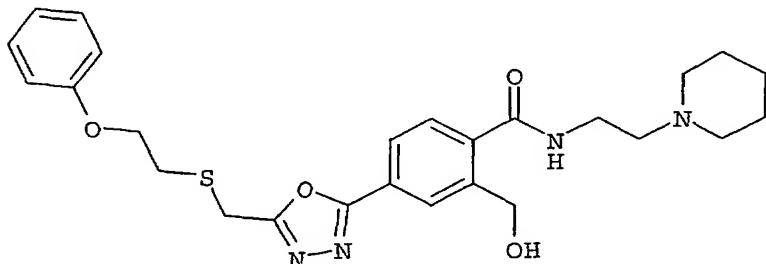


To a mixture of 4-carboxyphthalide (178 mg, 1 mmol), 2-phenoxythioacetic hydrazide hydrochloride (316 mg, 1.2 mmol), 4-(N,N-dimethylamino)phenyldiphenylphosphine (917 mg, 3 mmol), and triethylamine (607 mg, 6 mmol) in acetonitrile (10 mmol) was added carbon tetrachloride (770 mg, 5 mmol). The resultant mixture was stirred at room temperature overnight and concentrated. The residue was partitioned between ether (50 mL) and 2 M HCl (30 mL). The organic layer was washed with 2 M HCl (5 x 20 mL), dried (MgSO_4), and concentrated. The residue was triturated from methylene chloride and hexanes to give a white solid (186 mg, 51%).

10 The reaction was repeated on 3 mmol scale to give the same product (652 mg, 59%).

¹H NMR (CDCl_3) δ 8.16 (d, 1H, $J=8.1$ Hz), 8.13 (s, 1H), 8.02 (d, 1H, $J=7.8$ Hz), 7.22-7.26 (m, 2H), 6.93 (t, 1H, $J=7.3$ Hz), 6.86 (d, 2H, $J=8.0$ Hz), 5.37 (s, 2H), 4.20 (t, 2H, $J=5.8$ Hz), 4.09 (s, 2H), 3.05 (t, 2H, $J=5.9$ Hz). MS (ES+) m/e 369 (M+1).

b) 2-{{(2-Phenoxyethyl)thio)methyl}-5-{3-hydroxymethyl-4-[((2-piperidinoethyl)amino)carbonyl]phenyl}-1,3,4-oxadiazolo

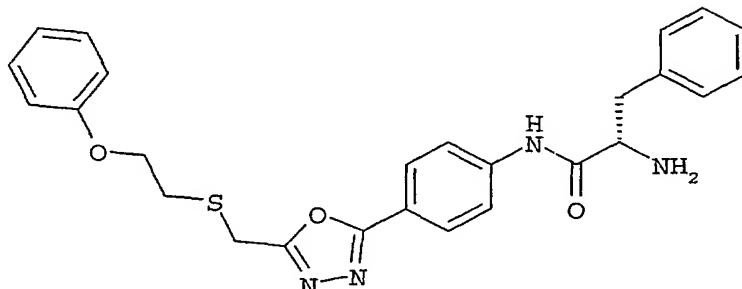


Lithium aluminum hydride (1 M in ether, 1 mL, 1 mmol) was diluted with tetrahydrofuran (1 mL) and N-(2-aminoethyl)piperidine (641 mg, 5 mmol) in tetrahydrofuran (1 mL) was added dropwise over 3 min. The resultant mixture was stirred at room temperature for 2 hr, diluted with tetrahydrofuran (4 mL), and 5-{{2-[(2-phenoxyethyl)thio)methyl]-1,3,4-oxadiazol-5-yl}phthalide (368 mg, 1 mmol) was added. Stirring was continued at room temperature overnight and tetrahydrofuran (5 mL), followed by 2 M NaOH (5 mL) was added. The mixture was stirred for 30 min, diluted with water (15 mL), and extracted with ethyl acetate (3 x 15 mL). The combined ethyl acetate extracts were washed with brine (15 mL), dried (MgSO_4), and concentrated. The residue was recrystallized from methylene chloride and hexanes (1:1) to give a white solid (280 mg, 56%).

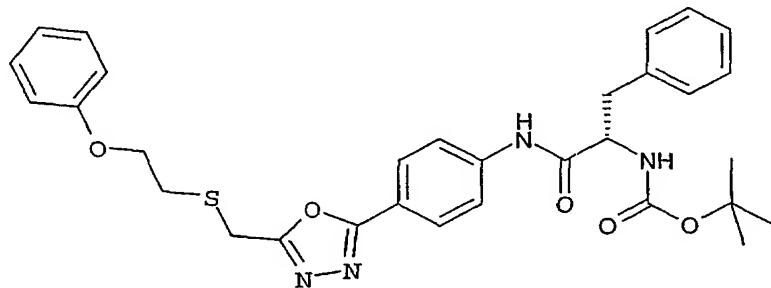
¹H NMR (CDCl_3) δ 8.02 (s, 1H), 8.0 (d, 1H, $J=8.0$ Hz), 7.64 (d, 1H, $J=7.7$ Hz), 7.22-7.26 (m, 2H), 7.10 (br s, 1H), 6.92 (t, 1H, $J=7.3$ Hz), 6.87 (d, 2H, $J=8.4$ Hz), 4.64 (s, 2H), 4.19 (t, 2H, $J=6.0$ Hz), 4.05 (s, 2H), 3.59 (dd, 2H, $J=8.2, 5.5$ Hz), 3.04 (t, 2H, $J=5.9$ Hz), 2.60 (t, 2H, $J=5.7$ Hz), 2.4-2.52 (m, 4H), 1.60-1.66 (m, 4H), 1.47-1.50 (m, 2H). IR (KBr, cm^{-1}) 3465, 3310, 2940, 2888, 2854, 1638, 1556, 1496, 1420, 1297, 1020, 750. MS (ES+) m/e 497 (M+1). Anal. Calcd for $\text{C}_{26}\text{H}_{32}\text{N}_4\text{O}_4\text{S}$: C, 62.88; H, 6.49; N, 11.28; S, 6.46. Found C, 63.27; H, 6.46; N, 11.14; S, 6.28.

Example 161

Preparation of 2-{{(2-Phenoxyethyl)thio]methyl}-5-[4-(2-benzyl-2-aminoacetamido)phenyl]-1,3,4-oxadiazole



- 5 a) 2-{{(2-Phenoxyethyl)thio]methyl}-5-[4-[2-benzyl-2-((tert-butoxycarbonyl)amino)acetamido]phenyl]-1,3,4-oxadiazole

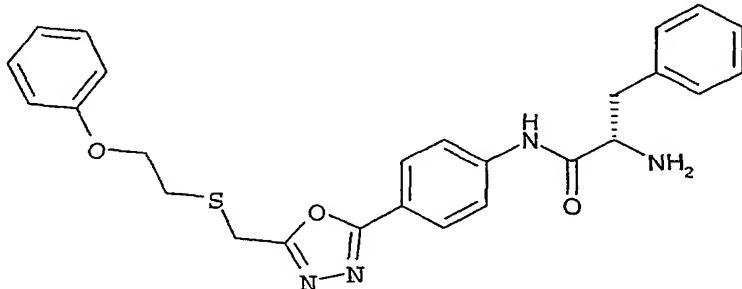


To a mixture of 2-{{(2-phenoxyethyl)thio]methyl}-5-(4-aminophenyl)-1,3,4-oxadiazole (327 mg, 1 mmol), Boc-L-phenylalanine (796 mg, 3 mmol), and 1-hydroxybenzotriazole (405 mg, 3 mmol) in tetrahydrofuran (25 mL) was added diisopropylcarbodiimide (379 mg, 3 mmol) and the mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate (25 mL), washed with 2 M NaOH (3 x 10 mL) and brine (25 mL), dried (MgSO_4), and concentrated. The residue was purified by chromatography (silica gel) to give a yellow solid (167 mg, 29%).

^1H NMR (CDCl_3) δ 7.93 (d, 2H, $J=8.4$ Hz), 7.80 (d, 2H, $J=8.4$ Hz), 7.22-7.32 (m, 7H), 6.93 (t, 1H, $J=7.5$ Hz), 6.87 (d, 2H, $J=7.7$ Hz), 5.08 (br s, 1H), 4.18 (t, 2H, $J=6.2$ Hz), 4.02 (s, 2H), 3.78 (t, 1H, $J=6.4$ Hz), 3.14 (d, 2H, $J=6.9$ Hz), 3.03 (t, 2H, $J=6.2$ Hz), 1.12 (s, 9H). MS (ES+) m/e 575 (M+1).

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- b) 2-{{(2-Phenoxyethyl)thio}methyl}-5-[4-(2-benzyl-2-aminoacetamido)phenyl]-1,3,4-oxadiazole

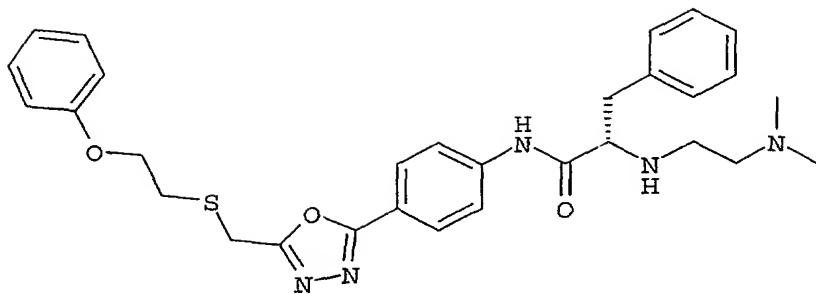


A mixture of 2-{{(2-phenoxyethyl)thio}methyl}-5-[4-[2-benzyl-2-((tert-
5 butoxycarbonyl)amino)acetamido]phenyl]-1,3,4-oxadiazole (144 mg, 0.25 mmol) and
25% trifluoroacetic acid in methylene chloride (2.5 mL) was stirred at room temperature
overnight and concentrated. The residue was taken up in methylene chloride (15 mL),
washed with 2 M NaOH (2 x 10 mL), dried (MgSO_4), and concentrated. The residue was
purified by chromatography (silica gel, 10% methanol/methylene chloride) to give a white
10 solid (74 mg, 60%).

^1H NMR (CDCl_3) δ 9.69 (s, 1H), 7.98 (d, 2H, $J=8.8$ Hz), 7.74 (d, 2H, $J=8.7$ Hz),
7.23-7.34 (m, 7H), 6.93 (t, 1H, $J=7.3$ Hz), 6.89 (d, 2H, $J=8.8$ Hz), 4.19 (t, 2H, $J=6.2$ Hz),
4.03 (s, 2H), 3.75 (dd, 1H, $J=9.5, 4.0$ Hz), 3.37 (dd, 2H, $J=13.9, 3.7$ Hz), 3.04 (t, 2H,
 $J=6.2$ Hz), 2.80 (dd, 1H, $J=13.9, 9.5$ Hz). IR (KBr, cm^{-1}) 3430, 3060, 2981, 2926, 1681,
15 1599, 1501, 1426, 1386, 1238, 1094, 744. MS (ES+) m/e 475 (M+1). Anal. Calcd for
 $\text{C}_{26}\text{H}_{26}\text{N}_4\text{O}_3\text{S}$: C, 65.80; H, 5.52; N, 11.81; S, 6.76. Found C, 65.70; H, 5.56; N, 11.68; S,
6.61.

Example 162

20 Preparation of (S)-2-{{(2-Phenoxyethyl)thio}methyl}-5-[4-[2-benzyl-2-(N',N'-
dimethylethylenediamino)acetamido]phenyl]-1,3,4-oxadiazole

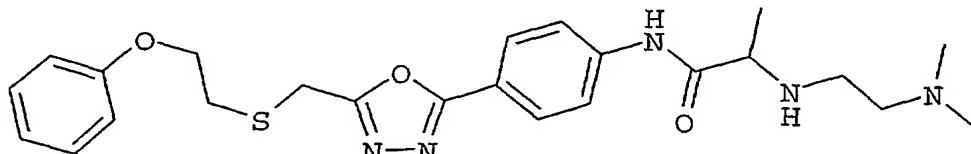


A mixture of 2-[(2-phenoxyethyl)thio]methyl-5-[4-(2-benzyl-2-aminoacetamido)phenyl]-1,3,4-oxadiazole (61 mg, 0.125 mmol), 2-(N,N-dimethylamino)ethylchloride hydrochloride (72 mg, 0.5 mmol), sodium carbonate (211 mg, 2 mmol), and sodium iodide (75 mg, 0.5 mmol) in ethanol (5 mL) was stirred under reflux overnight. The reaction mixture was poured into water (20 mL) and extracted with methylene chloride (3 x 10 mL). The combined methylene chloride extracts were dried (MgSO₄) and concentrated. The residue was purified by chromatography (silica gel, 10% methanol/methylene chloride) to give the desired product (30 mg, 44%) and recovered starting amine (13 mg, 21%).

¹H NMR (CDCl₃) δ 10.06 (s, 1H), 7.98 (d, 2H, J=8.5 Hz), 7.78 (d, 2H, J=8.8 Hz), 7.23-7.33 (m, 7H), 6.93 (t, 1H, J=7.3 Hz), 6.88 (d, 2H, J=8.4 Hz), 4.20 (t, 2H, J=6.0 Hz), 4.03 (s, 2H), 3.32-3.42 (m, 2H), 3.04 (t, 2H, J=6.2 Hz), 2.74 (dd, 1H, J=13.9, 10.2 Hz), 2.54-2.58 (m, 2H), 2.38 (m, 1H), 2.24 (m, 1H), 2.09 (s, 6H). MS (ES+) m/e 546 (M+1). Anal. Calcd for C₃₀H₃₅N₅O₃S: C, 66.03; H, 6.46; N, 12.83; S, 5.88. Found C, 66.18; H, 6.37; N, 12.71; S, 6.01.

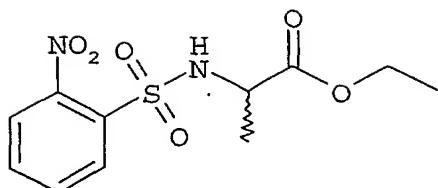
Example 163

Preparation of (+)-2-[(2-Phenoxyethyl)thio]methyl-5-{4-[2-methyl-2-(N',N'-dimethylethylenediamino)acetamido]phenyl}-1,3,4-oxadiazole



a) (+)-Ethyl 2-[(2-nitrobenzenesulfonyl)amino]propionate

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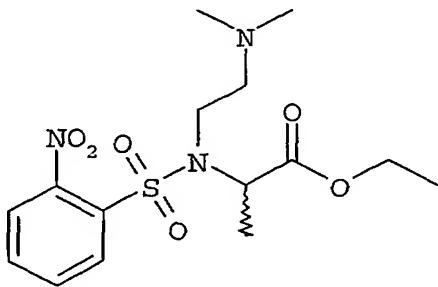


A solution of 2-nitrobenzenesulfonyl chloride (6.0 g, 27.1 mmol) and DL-alanine ethyl ester hydrochloride (5.0 g, 32.5 mmol) in methylene chloride (250 mL) was cooled in an ice/water bath. Triethylamine (9.5 mL, 67.8 mmol) was added dropwise over 3 min.

- 5 The reaction was stirred for 10 min in the ice/water bath, then at room temperature for 3 h. The mixture was extracted with 2N HCl (3x100 mL), dried (MgSO_4), filtered and concentrated to yield 8.1 g (98%) of a yellow solid.

¹H NMR (CDCl_3) δ 8.05 (m, 1H), 7.89 (m, 1H), 7.69 (m, 2H), 6.07 (d, 1H, $J=8$ Hz), 4.19 (m, 1H), 3.93 (dd, 2H, $J=14$ and 14 Hz), 1.45 (dd, 3H, $J=3$ and 6 Hz), 1.07 (dt, 3H, $J=14$ and 14 Hz). MS (ES+) m/e 303 ($M+1$).

- b) (+)-Ethyl 2-[N-(2-nitrobenzenesulfonyl)-N-(N',N'-dimethylamino)-1,2-ethanediamino]propionate



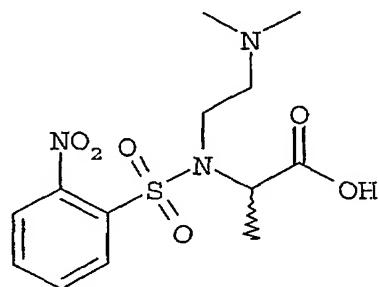
15 A solution of ethyl (+)-ethyl 2-[(2-nitrobenzenesulfonyl)amino]propionate (3.0 g, 10 mmol), N,N-dimethylethanamine (2.0 mL, 20 mmol) and triphenylphosphine (6.56 g, 25 mmol) in THF (100 mL) were cooled in an ice/water bath. Diethyl azodicarboxylate (4.0 mL, 25 mmol) was added dropwise over 3 min, stirred another 10 min, then stirred at room temperature for 16 h. The mixture was concentrated, diluted with methanol (20 mL) and loaded onto a column containing Bio-Rad 50W-X2 cation exchange resin (50 g, pre-washed 800 mL of methanol). The column was washed with methanol (800 mL) and methylene chloride (200 mL). The product was then eluted with 2N ammonia/methanol (500 mL) and concentrated to yield 3.34 g of a yellow oil. This material was diluted with

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ethyl acetate (50 mL), extracted with water (3x50 mL), dried (MgSO_4), filtered and concentrated to yield 2.92 g (78%) of a yellow oil.

¹H NMR (CDCl_3) δ 8.07 (m, 1H), 7.65 (m, 2H), 7.57 (m, 1H), 4.75 (m, 1H), 4.03 (m, 2H), 3.56 (m, 1H), 3.17 (m, 1H), 2.63 (m, 1H), 2.46 (m, 1H), 2.20 (s, 6H), 1.51 (d, 5 3H, $J=7$ Hz), 1.12 (t, 3H, $J=14$ Hz). MS (ES+) m/e 375 (M+1).

c) (+)-2-[N-(2-Nitrobenzenesulfonyl)-N-(N',N'-dimethylamino)-1,2-ethanediamino]propionic acid

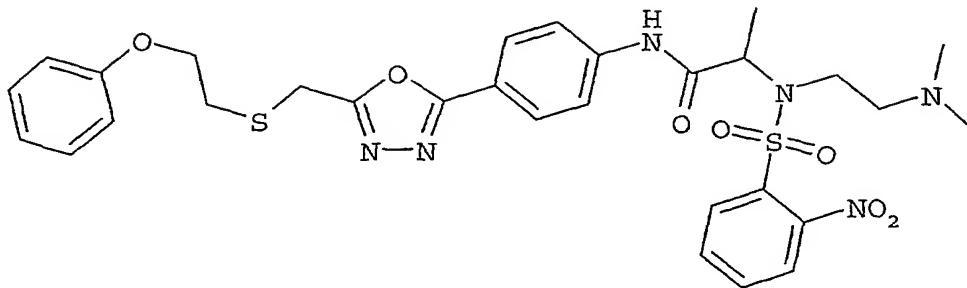


10 A solution of (+)-ethyl 2-[N-(2-nitrobenzenesulfonyl)-N-(N',N'-dimethylamino)-1,2-ethanediamino]propionate (2.92 g, 7.8 mmol) and aqueous 2 N NaOH (20 mL, 40 mmol) in tetrahydrofuran (14 mL) was stirred at room temperature for 2 h. The mixture was loaded onto a column of Bio-Rad AG1-X2 anionic exchange resin (40 g, pre-washed with 800 mL of water) and allowed to settle for 20 min before it was passed through the 15 column. The column was washed with water (800 mL) and 1,4-dioxane (600 mL). The product was then eluted with 4 N HCl in 1,4-dioxane and concentrated to yield 2.06 g (76%) of a yellow oil.

1 H NMR (DMSO-D6) δ 10.00 (br s, 1H), 8.17 (m, 1H), 7.80-7.92 (m, 3H), 4.55 (m, 1H), 4.15 (m, 1H), 3.80 (m, 1H), 3.75 (m, 2H), 2.75 (s, 6H), 1.45 (d, 2H, $J=7$ Hz).
20 MS (ES-) m/e 344 (M-1).

d) (+)-2-[(2-Phenoxyethyl)thio]methyl-5-{4-[(2-(N',N'-dimethyl-N-(2-nitrobenzenesulfonyl)-1,2-ethanediamino)propionyl)amino]phenyl}-1,3,4-oxadiazole

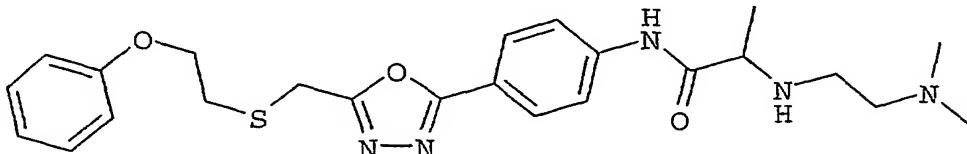
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A solution of (+)-2-[(2-nitrobenzenesulfonyl)-N-(N',N'-dimethylamino)-1,2-ethanediamino]propionic acid (345 mg, 1 mmol) and 2-{[(2-phenoxyethyl)thio]methyl}-5-(4-aminophenyl)-1,3,4-oxadiazole (327 mg, 1 mmol) in anhydrous pyridine (3.0 mL) was cooled in an ice-salt water bath under nitrogen. Phosphorus oxychloride (0.15 mL, 1.6 mmol) was added dropwise and the cooled reaction stirred for 3 h. The reaction was quenched with water (10 mL) and extracted with ethyl acetate (3x10 mL). The combined organic phase was extracted with saturated aqueous sodium bicarbonate (3x10 mL), water (3x10 mL) and brine (3x10 mL), dried (MgSO_4), filtered and concentrated. The residue was co-evaporated with toluene (3x5 mL) to remove any lingering pyridine. This material was purified by preparative TLC (5% methanol/methylene chloride) to yield 147 mg (22%) of a brown oil.

^1H NMR (CDCl_3) δ 8.59 (br s, 1H), 8.16 (d, 1H, $J=9$ Hz), 7.97 (d, 2H, $J=9$ Hz), 7.63-7.75 (m, 5H), 7.25 (m, 2H), 6.93 (m, 1H), 6.87 (d, 2H, $J=8$ Hz), 4.18 (m, 3H), 4.02 (s, 2H), 3.91 (m, 1H), 3.42 (m, 1H), 3.02 (m, 2H), 2.55 (m, 1H), 2.43 (m, 1H), 2.24 (s, 6H), 1.40 (t, 3H, $J=14$ Hz). MS (ES+) m/e 655 (M+1).

e) (+)-2-{[(2-Phenoxyethyl)thio]methyl}-5-{4-[2-methyl-2-(N',N'-dimethylethylenediamino)acetamido]phenyl}-1,3,4-oxadiazole



20

A mixture of (+)-2-{[(2-phenoxyethyl)thio]methyl}-5-{4-[(2-(N',N'-dimethyl-N-(2-nitrobenzenesulfonyl)-1,2-ethanediamino)propionyl)amino]phenyl}-1,3,4-oxadiazole (147 mg, 0.22 mmol), benzenethiol (0.04 mL, 0.39 mmol) and potassium carbonate (93 mg, 0.67 mmol) was stirred in N,N-dimethylformamide (2.0 mL) at room temperature for

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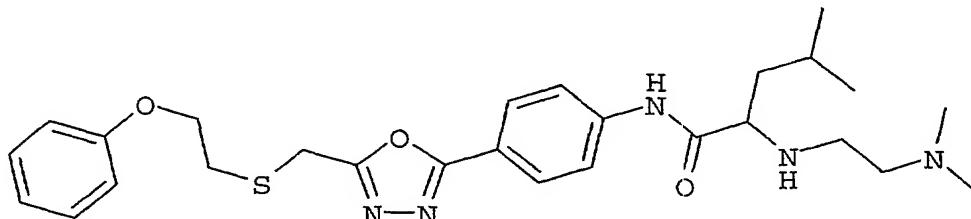
1 h. The mixture was diluted with ethyl acetate (40 mL), extracted with water (5x10 mL), dried (MgSO_4), filtered and concentrated to yield 182 mg of a brown oil. This residue was purified by preparative TLC (10% methanol/methylene chloride) to yield 35 mg (33%) of a colorless oil.

5 ^1H NMR (CDCl_3) δ 9.97 (s, 1H), 7.97 (d, 2H, $J=8$ Hz), 7.76 (d, 2H, $J=8$ Hz), 7.26 (m, 2H), 6.93 (dd, 1H, $J=7$ and 8 Hz), 6.88 (d, 2H, $J=8$ Hz), 4.19 (t, 2H, $J=12$ Hz), 4.02 (s, 2H), 3.26 (m, 1H), 3.04 (t, 2H, $J=12$ Hz), 2.81 (m, 1H), 2.64 (m, 1H), 2.47 (m, 1H), 2.37 (m, 1H), 2.24 (s, 6H), 1.40 (d, 2H, $J=7$). IR (film, cm^{-1}) 3421, 3071, 2977, 2938, 1683, 1603, 1499, 1499, 1413, 1242, 732. MS (ES+) m/e 470 (M+1). Anal. Calcd for
10 $\text{C}_{24}\text{H}_{31}\text{N}_5\text{O}_3\text{S}$: C, 61.38; H, 6.65; N, 14.91; S, 6.83. Found C, 61.86; H, 6.62; N, 15.06; S, 6.41.

Example 164

Preparation of (+)-2-{{[(2-Phenoxyethyl)thio]methyl}-5-{4-[2-isobutyl-2-(N',N'-dimethylethylenediamino)acetamido]phenyl}-1,3,4-oxadiazole

15



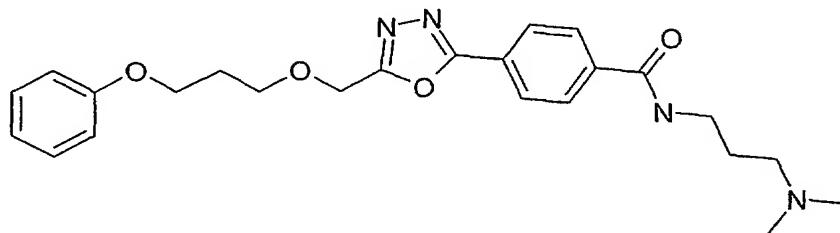
This compound was prepared similarly to (+)-2-{{[(2-phenoxyethyl)thio]methyl}-5-{4-[2-methyl-2-(N',N'-dimethylethylenediamino)acetamido]phenyl}-1,3,4-oxadiazole from DL-alanine ethyl ester hydrochloride.

20 ^1H NMR (CDCl_3) \square 9.98 (s, 1H), 7.96 (d, 2H, $J=9$ Hz), 7.76 (d, 2H, $J=9$ Hz), 7.25 (m, 2H), 6.93 (dd, 1H, $J=7$ and 8 Hz), 6.87 (d, 2H, $J=8$ Hz), 4.19 (t, 2H, $J=12$ Hz), 4.02 (s, 2H), 3.18 (m, 1H), 3.04 (t, 2H, $J=12$ Hz), 2.76 (m, 1H), 2.65 (m, 1H), 2.47 (m, 1H), 2.39 (m, 1H), 2.24 (s, 6H), 1.65-1.78 (m, 2H), 1.48 (m, 1H), 0.96 (dd, 6H, $J=2$ and 9 Hz). IR (film, cm^{-1}) 2958, 2867, 2250, 1684, 1601, 1505, 1240, 909, 734, 650. MS (ES+) m/e 512 (M+1). Anal. Calcd for $\text{C}_{27}\text{H}_{37}\text{N}_5\text{O}_3\text{S}$: C, 63.38; H, 7.29; N, 13.69; S, 6.27. Found C, 63.70; H, 6.73; N, 13.79; S, 5.93.

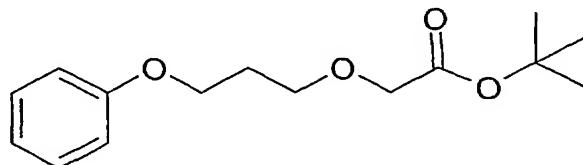
Example 165

-327-

Preparation of N-(3-Dimethylamino-propyl)-4-[5-(3-phenoxy-propoxymethyl)-[1,3,4]oxadiazol-2-yl]-benzamide



a) (3-Phenoxy-propoxy)-acetic acid tert-butyl ester

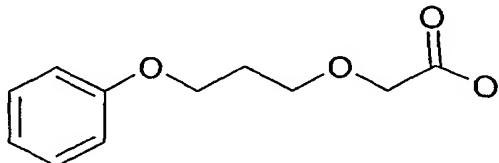


5

To a solution of 3-phenoxypropanol (5 g, 32.8 mmol) in 30 mL toluene was added tert-butyldibromoacetate (19.2 g, 99 mmol) and tetrabutylammonium hydrogen sulfate (2.8 g, 8.2 mmol). The mixture was cooled to 0°C and treated with 25 mL 50% aqueous NaOH. After stirring for 10 minutes at 0°C the cooling bath was removed and the reaction 10 was stirred at ambient temperature for 2 hours. It was diluted with 50 mL toluene and the layers were separated. The aqueous layer was extracted with 50 mL toluene and the combined organic layer was dried over MgSO₄ before concentrating to dryness. The resulting colorless oil was purified by chromatography using EtOAc in hexanes to recover 6.1 g (23 mmol, 69%) of the desired product as an oil. MS (ES) m/e 378

15 ¹H NMR (CDCl₃) δ 7.29-7.25 (m, 2H), 6.95-6.89 (m, 3H), 4.11-4.07 (m, 2H), 3.97 (s, 2H), 3.72-3.69 (m, 2H), 2.11-2.08 (m, 2H,) and 1.47 (s, 9H).

b) (3-Phenoxy-propoxy)-acetic acid



20 (3-Phenoxy-propoxy)-acetic acid tert-butyl ester (7.6 g, 29 mmol) was mixed with 18 g anisole and 50 mL CH₂Cl₂ then treated with 25 mL TFA. The mixture was stirred at ambient temp overnight, concentrated to dryness under vacuum and purified by

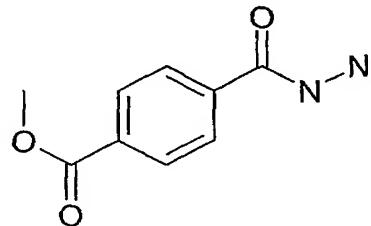
-328-

chromatography using MeOH in CHCl₃ to recover 5.5 (26 mmol, 90%) of the desired product as an oil. MS (ES) m/e 211

¹H NMR (CDCl₃) δ 10.55 (bs, 1H), 7.3-7.6 (m, 2H), 6.97-6.90 (m, 3H), 4.15 (s, 2H), 4.14-4.10 (m, 2H), 3.78-3.75 (m, 2H), 2.14-2.08 (m, 2H).

5

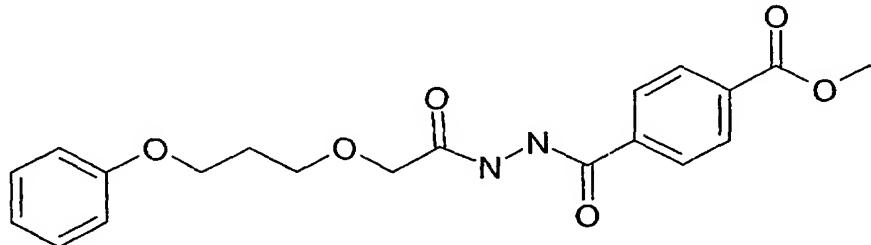
c) 4-Hydrazinocarbonyl-benzoic acid methyl ester



A mixture of dimethyl terephthalate (11 g, 57 mmol) and 350 mL MeOH was treated with 2 mL (62 mmol) of anhydrous hydrazine. The mixture was refluxed for 4 hours, cooled to room temp and filtered. The filtrate was allowed to stand at room temp for several hours then refiltered. The second filtrate was concentrated to dryness, mixed with 200 mL THF, refluxed for several minutes then allowed to stand at room temperature for several hours. The solid was filtered to recover 3.9 g (20 mmol, 35%) product as white crystals. MS (ES) m/e 211

10 15 ¹H NMR (DMSO-d₆) δ 9.95 (s, 1H), 8.0-7.98 (m, 2H), 7.92-7.90 (m, 2H), 4.56 (s, 2H), and 3.30 (s, 3H).

d) 4-{N'-[2-(3-Phenoxy-propoxy)-acetyl]-hydrazino}-benzoic acid methyl ester

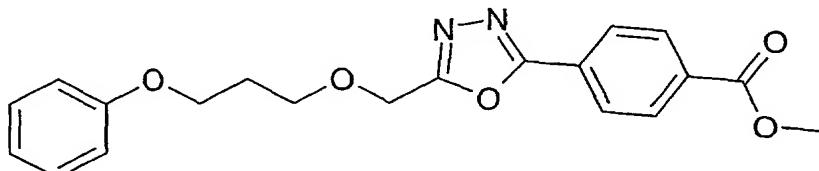


20 A mixture of (3-phenoxy-propoxy)-acetic acid (3 g, 14.3 mmol) in 25 mL CH₂Cl₂ was treated with an excess (1 mL) oxalyl chloride and 1 drop of DMF then stirred overnight. After concentration to dryness under vacuum, the residue was dissolved in 10 mL CH₂Cl₂ and added to a cold (0°C) mixture of 125 mL pyridine and the 4-

hydrazinocarbonyl-benzoic acid methyl ester. The reaction was stirred overnight at ambient temperature, concentrated to dryness under vacuum and purified by chromatography using EtOAc in hexanes to recover 2.7 g of oil which crystallized.

¹H NMR (CDCl₃) δ 9.36-9.35 (m, 1H), 9.11-9.09 (m, 1H), 8.07-8.03 (m, 2H),
5 7.82-7.80 (m, 2H), 7.28-7.22 (m, 2H), 6.94-6.86 (m, 3H), 4.12-4.06 (m, 4H), 3.94 (s, 3H),
3.79-3.76 (m, 2H), and 2.15-2.07 (m, 2H).

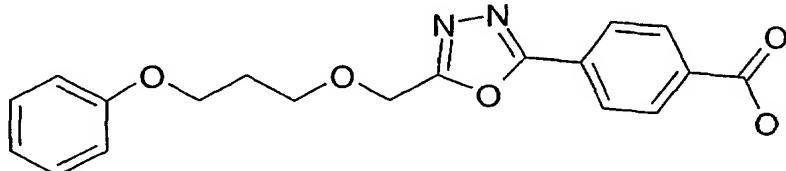
e) 4-[5-(3-Phenoxy-propoxymethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid methyl ester



10 A mixture of 4-{N'-[2-(3-Phenoxy-propoxy)-acetyl]-hydrazino}-benzoic acid methyl ester (2.3 g, 6 mmol) and 25 mL SOCl₂ was refluxed overnight and concentrated to dryness under vacuum. Residual SOCl₂ was removed by mixing with toluene and reconcentrating to an oil. After dissolving in 16 mL CH₂Cl₂ and 4 mL MeOH, it was treated with 3 mL 2 M trimethylsilyldiazomethane in hexanes, reconcentrated to dryness
15 and purified by silica gel chromatography using EtOAc in hexanes to recover 0.8 g of product.

¹H NMR (CDCl₃) δ 8.15-8.08 (m, 4H), 7.24-7.21 (m, 2H), 6.91-6.84 (m, 3H),
4.79 (s, 2H), 4.08-4.06 (m, 2H), 3.96 (s, 3H), 3.82-3.79 (m, 2H), 2.13-2.07 (m, 2H).

20 f) 4-[5-(3-Phenoxy-propoxymethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid



4-[5-(3-Phenoxy-propoxymethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid methyl ester (0.8 g, 2.3 mmol) was dissolved in 50 mL THF, treated with 3.5 mL 1 M aqueous LiOH, and stirred overnight at ambient temperature. The reaction was neutralized with 3.5 mL 1 N HCl, mixed with 20 mL brine and extracted twice with 20 mL EtOAc. The extracts

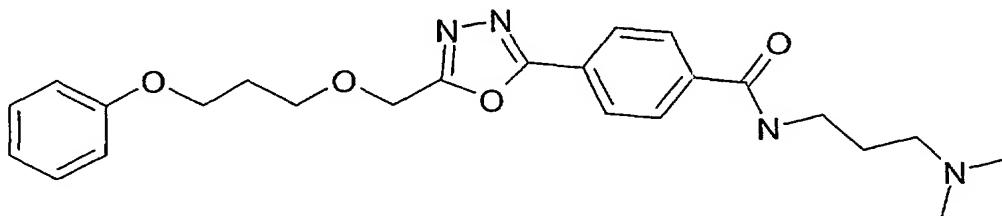
-330-

were dried over MgSO₄ and concentrated to 550 mg (1.6 mmol, 68%) of a white solid which was used as isolated in the next procedure.

¹H NMR (DMSO-d₆) δ 8.15-8.08 (m, 4H), 7.24-7.21 (m, 2H), 6.91-6.84 (m, 3H), 4.08-4.06 (m, 2H), 3.96 (s, 3H), 3.82-3.79 (m, 2H), 2.13-2.07 (m, 2H).

5

g) N-(3-Dimethylamino-propyl)-4-[5-(3-phenoxy-propoxymethyl)-[1,3,4]oxadiazol-2-yl]-benzamide



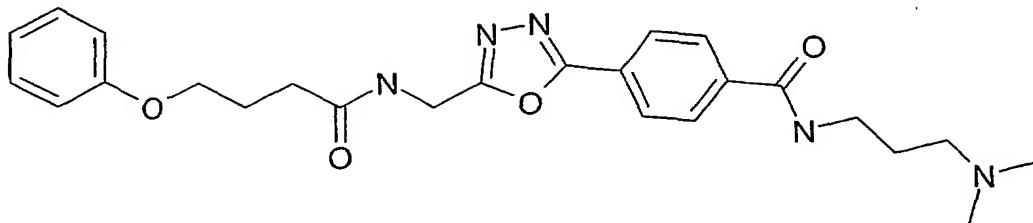
4-[5-(3-Phenoxy-propoxymethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid (500 mg, 1.4 mmol) was converted to it's acid chloride by mixing with 50 mL CH₂Cl₂, 2 mL oxalyl chloride and 2 drops of DMF and stirring for 1 hour. After concentration to dryness it was re-dissolved in 10 mL CH₂Cl₂ and added to a cold mixture of 3-dimethylaminopropylamine (317 mg, 3.1 mmol) in 30 mL CH₂Cl₂. The reaction was stirred at 0°C for 1 hour, concentrated to dryness then purified by silica gel chromatography using MeOH in CHCl₃ to recover 250 mg white solid.

¹H NMR (CDCl₃) δ 8.81 (s, 1H), 8.10-8.07 (m, 2H), 7.88-7.86 (m, 2H), 7.25-7.22 (m, 2H), 6.92-6.85 (m, 3H), 4.78(s, 2H), 4.09-4.06 (m, 2H), 3.82-3.79 (m, 2H), 3.62-3.58 (m, 2H), 2.55-2.52 (m, 2H), 2.3 (s, 6H), 2.13-2.07 (m, 2H), 1.81-1.75 (m, 2H).
Anal. Calcd for C₂₄H₃₀N₄O₄·0.2C₄H₁₀O·0.1H₂O: C, 65.19; H, 7.15; N, 12.26. Found C, 65.33; H, 6.86; N, 12.60.

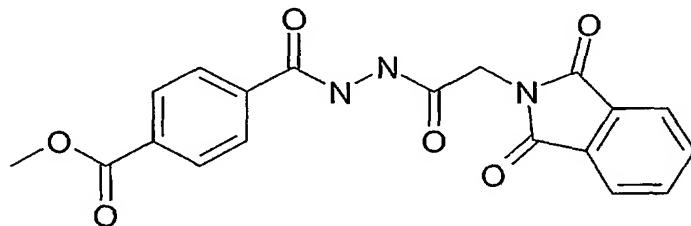
Example 166

Preparation of N-(3-Dimethylamino-propyl)-4-{5-[(4-phenoxy-butyrylamino)-methyl]-[1,3,4]oxadiazol-2-yl}-benzamide

-331-



- a) 4-{N'-[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-acetyl]-hydrazinocarbonyl}-benzoic acid methyl ester

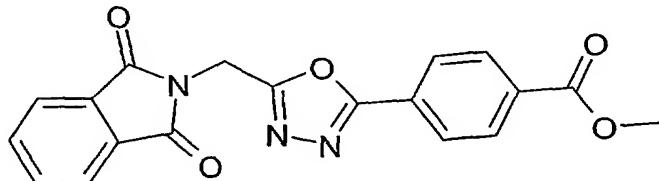


5 Starting from 4-hydrazinocarbonyl-benzoic acid methyl ester and N-phthaloylglycine, this compound was prepared in 69% yield in a similar manner as exemplified in example 165 d.

10 ^1H NMR (DMSO-d₆) δ 10.66(s, 1H), 10.45 (s, 1H), 8.05-8.03 (m, 2H), 7.96-7.91 (m, 4H), 7.88-7.85 (m, 2H), 4.34 (s, 2H), 3.86 (s, 3H) MS (ES) m/e 382.

10

- b) 4-[5-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid methyl ester



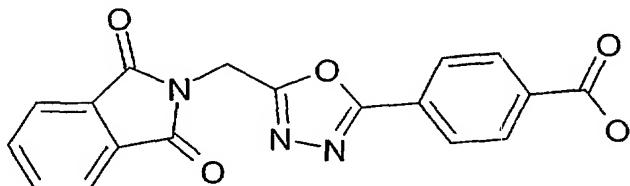
15 4-{N'-[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-acetyl]-hydrazinocarbonyl}-benzoic acid methyl ester (5 g, 13.11 mmol) was mixed with 100 mL SOCl₂ and refluxed over night. Concentration under vacuum gave a solid which was triturated with MeOH to recover 3 g (8.3 mmol, 63%) of the product as a white solid.

20 ^1H NMR (DMSO-d₆) δ 8.14-8.07 (m, 4H), 7.96-7.94 (m, 2H), 7.93-7.87 (m, 2H), 5.15 (s, 2H), 3.87 (s, 3H).

20

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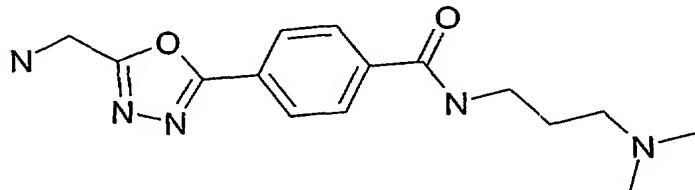
- c) 4-[5-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid



A mixture of 4-[5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid methyl ester (6 g, 16.5 mmol), thiophenol (3.6 g, 33 mmol), Potassium fluoride (1.9 g, 33 mmol) and N-methylpyrrolidinone (60 mL) was heated in a sealed tube at 180°C for 60 hours. The reaction was poured into 200 mL brine, diluted with 40 mL 5N HCl and extracted 3 times with 200 mL EtOAc. The combined extracts was dried over MgSO₄ and concentrated to dryness under vacuum. The residue was mixed with 50 mL CHCl₃ and filtered to recover 3.5 g solid.

¹H NMR (DMSO-d6) δ 12.0 (t, 1H), 8.1-8.0 (m, 2H), 7.95-7.85 (m, 2H), 7.8-7.7 (m, 1H), 7.6-7.5 (m, 1H), 7.4-7.3 (m, 2H), 7.7-7.8 (m, 2H). MS (ES) m/e 350.

- d) 4-(5-Aminomethyl-[1,3,4]oxadiazol-2-yl)-N-(3-dimethylamino-propyl)-benzamide



A mixture of 4-[5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-[1,3,4]oxadiazol-2-yl]-benzoic acid (4 g, 11.45 mmol), 3-dimethylaminopropyl amine (1.4 g, 13.7 mmol) and triethylamine (2.3 g, 22.9 mmol) in 100 mL dry DMF was cooled to 0°C and treated with dicyclohexylcarbodiimide (2.8 g, 13.7 mmol) and hydroxy benzotriazole (1.86 g, 13.7 mmol). The cooling bath was removed and the reaction was stirred for 2 hours before adding an additional 1 g (4.8 mmol) of dicyclohexylcarbodiimide. After stirring an additional 18 hours it was concentrated to dryness under vacuum, mixed with 250 mL CHCl₃ and filtered. The filtrate was purified by 2 chromatographies on silica using

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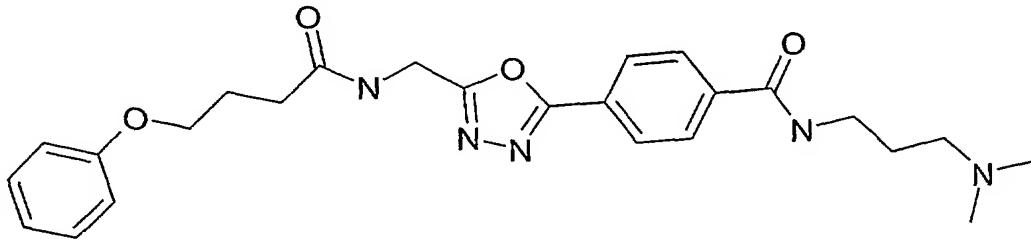
CHCl₃ and MeOH then THF, Hexanes and triethylamine to give 2 g of a solid. This was further purified using an ion exchange column to recover 1.7 g of an oil.

The above oil was dissolved in 50 mL EtOH and treated with 1 mL hydrazine monohydrate. After refluxing for 15 minutes, the reaction was concentrated to dryness, 5 mixed with 30 mL MeOH and filtered. The filtrate was purified by ion exchange chromatography to recover 1.2 g of a solid.

¹H NMR (CDCl₃) δ 8.75-8.65 (m, 1H), 8.10-8.0 (m, 4H), 3.95 (s, 2H), 3.3-3.25 (m, 4H), 2.3-2.25 (m, 2H), 2.15 (s, 6H), 1.7-1.6 (m, 2H).

Anal. Calcd for C₁₅H₂₁N₅O₂: C, 59.39; H, 6.98; N, 23.01. Found C, 59.11; H, 7.04; N, 10 22.78. MS (ES) m/e 304

e) N-(3-Dimethylamino-propyl)-4-{5-[(4-phenoxy-butyrylamino)-methyl]-[1,3,4]oxadiazol-2-yl}-benzamide



15 A mixture of the 4-(5-aminomethyl-[1,3,4]oxadiazol-2-yl)-N-(3-dimethylamino-propyl)-benzamide (150 mg, 0.5 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (147 mg, 0.74 mmol), 3-phenoxybutyric acid (133 mg, 0.74 mmol) and triethylamine (200 mg, 2 mmol) in 20 mL dry DMF was stirred for 4 hours. Concentrated to an oil under vacuum, mixed with CHCl₃ and purified by chromatography on silica 20 using a mixture of CHCl₃, MeOH and ammonium hydroxide to recover 78 mg (.17 mmol, 33%) of a white solid. MS (ES) m/e 304

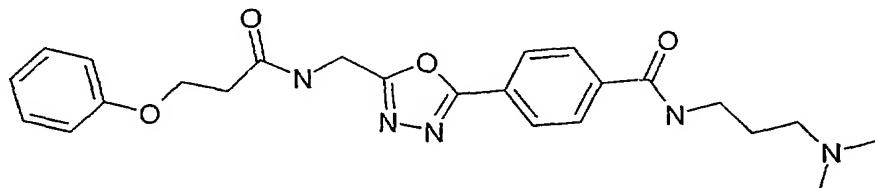
¹H NMR (CDCl₃) δ 8.92 (s, 1H), 8.03-8.01 (m, 2H), 7.84-7.82 (m, 2H), 7.27-7.23 (m, 2H), 6.94-6.86 (m, 3H), 6.63-6.60 (m, 1H), 4.77-4.75 (m, 2H), 4.05-4.02 (m, 2H) 25 3.60-3.56 (m, 2H), 2.56-2.51 (m, 4H), 2.30 (s, 6H), 2.22-2.15 (m, 2H), 1.8-1.74 (m, 2H).

Anal. Calcd for C₂₅H₃₁N₅O₄: C, 64.50; H, 6.73; N, 15.22. Found C, 64.50; H, 6.71; N, 15.04.

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Example 167

Preparation of N-(3-Dimethylamino-propyl)-4-{5-[(3-phenoxy-propionylamino)-methyl]-[1,3,4]oxadiazol-2-yl}-benzamide



Starting from 3-phenoxy propionic acid and 4-(5-aminomethyl-[1,3,4]oxadiazol-2-yl)-N-(3-dimethylamino-propyl)-benzamide this compound was prepared in 13% yield using the procedure exemplified in Example 166 e.

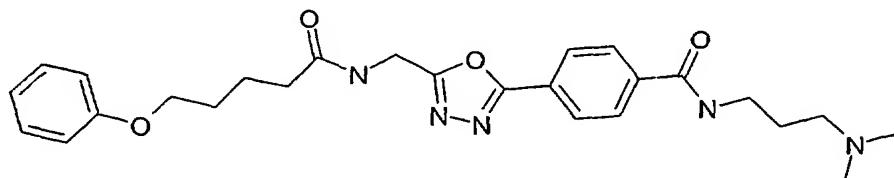
MS (ES) m/e 452

¹H NMR (CDCl₃) δ 8.92 (s, 1H), 8.03-8.01 (m, 2H), 7.84-7.82 (m, 2H), 7.29-7.25 (m, 2H), 6.98-6.90 (m, 4H), 4.81-4.79 (m, 2H), 4.32-4.30 (m, 2H), 3.59-3.48 (m, 2H), 2.82-2.79 (m, 2H), 2.54-2.51 (m 2H), 2.31 (s, 6H), 1.80-1.74 (m, 2H). Anal. Calcd for C₂₄H₃₀N₄O₄·0.2C₄H₁₀O·0.5H₂O: C, 62.59; H, 6.57; N, 15.21. Found C, 62.93; H, 6.27; N, 15.23.

15

Example 168

Preparation of N-(3-Dimethylamino-propyl)-4-{5-[(5-phenoxy-pentanoylamino)-methyl]-[1,3,4]oxadiazol-2-yl}-benzamide

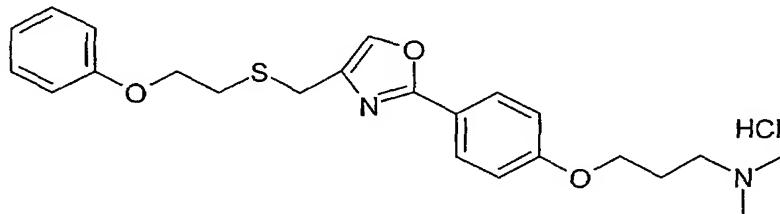


Starting from 3-phenoxy butyric acid and 4-(5-aminomethyl-[1,3,4]oxadiazol-2-yl)-N-(3-dimethylamino-propyl)-benzamide this compound was prepared in 22 % yield using the procedure exemplified in Example 166 e.

MS (ES) m/e 480. ¹H NMR (CDCl₃) δ 8.92 (s, 1H), 8.04-8.02 (m, 2H), 7.84-7.82 (m, 2H), 7.28-7.23 (m, 2H), 6.94-6.85 (m, 3H), 6.57 (s, 1H), 4.76-4.75 (m, 2H), 4.00-3.97 (m, 2H), 3.60-3.56 (m, 2H), 2.54-2.51 (m, 2H), 2.43-2.40 (m 2H), 2.30 (s, 6H), 1.92-1.84 (m, 4H), 1.80-1.74 (m, 2H). Anal. Calcd for C₂₆H₃₃N₅O₄·0.2H₂O: C, 64.63; H, 6.96; N, 14.50. Found C, 64.37; H, 6.76; N, 14.41.

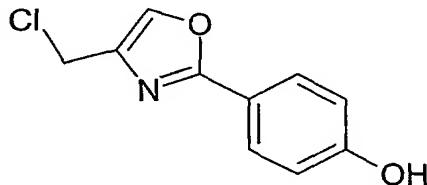
EXAMPLE 169

Preparation of Dimethyl-(3-{4-[4-(2-phenoxy-ethylsulfanylmethyl)-oxazol-2-yl]-phenoxy}-propyl)-amine Hydrochloride



5

a) 4-(4-Chloromethyl-oxazol-2-yl)-phenol



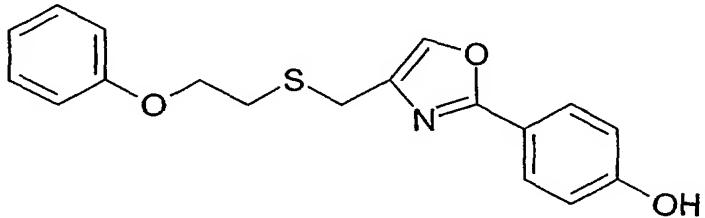
A solution of 4-hydroxy-benzamide (3.20 g, 23.33 mmol) and 1,3-dichloro acetone (5.93 g, 46.66 mmol) in 40 mL dimethylformamide was warmed to 120°C for 4 h.

10 The reaction mixture was allowed to cool to room temperature and poured into 50 g of ice/water. The resulting precipitate was filtered and dried in vacuo to afford 3.98 g (82%) 2-(4-hydroxyphenyl)-4-chloromethyl-oxazole as a white solid.

¹H NMR (DMSO-D₆, 300 MHz): δ 10.12 (s, 1H), 8.15 (s, 1H), 7.81 (d, 2H, J=9 Hz), 6.89 (d, 2H, J=9 Hz), 4.70 (s, 2H). MS (MH⁺) 210.

15

b) 4-[4-(2-Phenoxy-ethylsulfanylmethyl)-oxazol-2-yl]-phenol

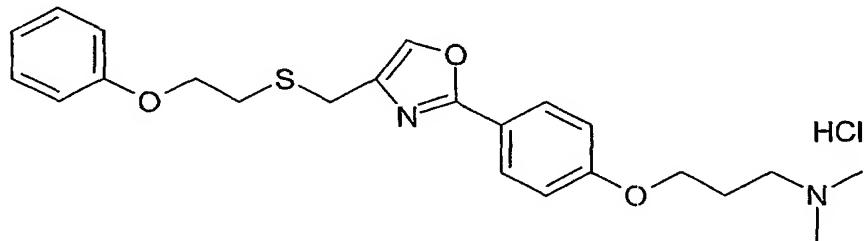


A solution of sodium hydride (200 mg, 8.34 mmol) in ethanol (47 mL) was treated with 2-phenoxy-ethanethiol (1.17 g, 7.59 mmol) in 5 mL ethanol at room temperature and 20 stirred for 10 minutes. 4-(4-Chloromethyl-oxazol-2-yl)-phenol (1.99 g, 9.48 mmol) was added and stirring was continued for 16 hours. The solvent was evaporated in vacuo and

the remains were poured into 50 mL water. The precipitate was filtered and dried in vacuo. The solid was stirred in 8 mL solvent mixture of hexane and tert.-butyl methylether (10 : 1), and dried again in vacuo to afford 2.13 g (86%) 4-[4-(2-phenoxy-ethylsulfanylmethyl)-oxazol-2-yl]-phenol as a white solid.

5 ¹H NMR (DMSO-D₆, 300 MHz): δ 10.18 (br s, 1H), 7.95 (s, 1H), 7.78 (d, 2H, J=9 Hz), 7.27 (d, 2H, J=12 Hz), 6.96 - 6.85 (m, 5H), 4.17 (t, 2H, J=7 Hz), 3.76 (s, 2H), 2.92 (t, 2H, J=7 Hz). MS (MH⁺) 328.

c) Dimethyl-(3-{4-[4-(2-phenoxy-ethylsulfanylmethyl)-oxazol-2-yl]-phenoxy}-propyl)-amine Hydrochloride

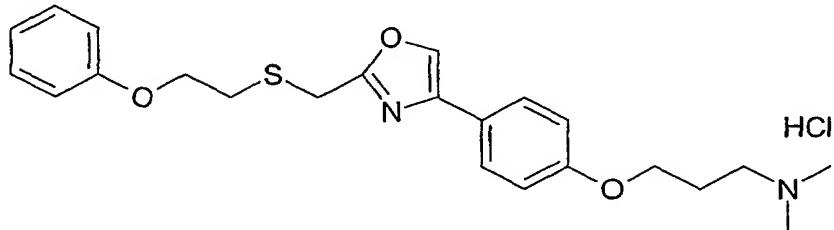


A suspension of 4-[4-(2-phenoxy-ethylsulfanylmethyl)-oxazol-2-yl]-phenol (524 mg, 1.60 mmol), dimethyl 3-chloro-propyl-amine hydrochloride (304 mg, 1.92 mmol), and potassium carbonate (531 mg, 3.84 mmol) in dimethylformamide (20 mL) was heated 15 at 80°C for 14 hours. The solvent was removed in vacuo and the remains partitioned between water and methylene chloride. The organic layer was dried over sodium sulfate and evaporated. The remaining oil was purified by chromatography on silica gel (elution with gradient methylene chloride/ethanol containing 10% ammonia) to afford a white solid. The solid was dissolved in 10 mL dioxane and treated with 0.1 mL 4M HCl in 20 dioxane and stirred for 10 minutes. Ether was added and the precipitation filtered and dried in vacuo to afford 204 mg (28%) of dimethyl-(3-{4-[4-(2-phenoxy-ethylsulfanylmethyl)-oxazol-2-yl]-phenoxy}-propyl)-amine as a white solid.

1 ¹H NMR (DMSO-D₆, 300 MHz): δ 10.42 (br s, 1H), 8.01 (s, 1H), 7.90 (d, 2H, J=9 Hz), 7.28 (t, 2H, J=8 Hz), 7.09 (d, 2H, J=9 Hz), 6.99 – 6.88 (m, 3H), 4.22 – 4.10 (m, 4H), 3.78 (s, 2H), 3.26 – 3.17 (m, 2H), 2.93 (t, 2H, J=7 Hz), 2.79 (s, 3H), 2.78 (s, 3H), 2.23 – 2.12 (m, 2H). MS (MH⁺) 413.

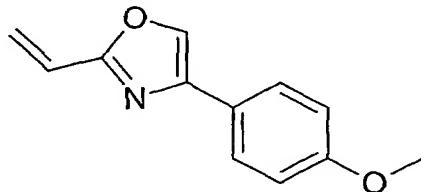
EXAMPLE 170

Preparation of Dimethyl-(3-{4-[2-(2-phenoxy-ethylsulfanyl-methyl)-oxazol-4-yl]-phenoxy}-propyl)-amine



5

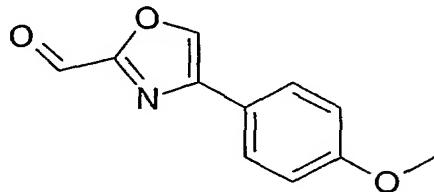
a) 4-(4-Methoxy-phenyl)-2-vinyl-oxazole



A solution of ω -bromo acetophenone (11.93 g, 52.08 mmol), 2,6 di-tert.-butyl-4-methyl-phenol as a stabilizer (1.15 g, 5.21 mmol), and acryl amide (7.40 g, 104.16 mmol) were dissolved in 360 mL dimethylformamide and heated at 150°C for 4 hours. The solvent was evaporated and the remaining oil dissolved in 200 mL ethyl acetate and washed with 150 mL water. The organic layer was dried over sodium sulfate and evaporated and the remaining oil purified by chromatography on silica gel (elution with gradient hexane/ethyl acetate) to afford 5.59 g (53%) of 4-(4-methoxy-phenyl)-2-vinyl-oxazole as a white solid.

¹H NMR (CDCl₃, 300 MHz): δ 7.76 (s, 1H), 7.67 (d, 2H, J=9 Hz), 6.94 (d, 2H, J=9 Hz), 6.65 (dd, 1H, J=18 Hz, J=11 Hz), 6.22 (d, 1H, J=18 Hz), 5.65 (d, 1H, J=11 Hz), 3.34 (s, 3H). MS (MH⁺) 202.

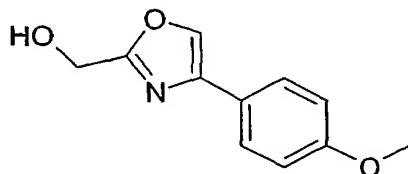
b) 4-(4-Methoxy-phenyl)-oxazole-2-carbaldehyde



A solution of 4-(4-methoxy-phenyl)-2-vinyl-oxazole (3.06 g, 15.21 mmol), N-methyl-morpholine N-oxide(2.16 g, 15.97 mmol), hydrochinidine-(1,4-phthalazindiyldiether)(116 mg, 1.49 mmol) in 70 mL acetone : water (4 : 1) was treated with 4 mL of 0.079 M aqueous osmium tetroxide solution and was stirred at room temperature for 4 hours. The solvent was evaporated in vacuo and remaining oil was dissolved in 150 mL methylene chloride and washed with 50 mL 10 % aqueous sodium sulfite solution. The organic layer was dried over sodium sulfate and evaporated. The remaining oil was dissolved in 50 mL tert.-butyl methylether and 50 mL water and treated with sodium meta periodate and stirred for 4 hours. The organic layer was than separated, dried over sodium sulfate and evaporated to afford 1.5 g (49%) of 4-(4-methoxy-phenyl)-oxazole-2-carbaldehyde as a colourless oil.

¹H NMR (CDCl₃, 300 MHz): δ 9.82 (s, 1H), 8.04 (s, 1H), 7.73 (d, 2H, J=9 Hz), 6.98 (d, 2H, J=9 Hz), 3.87 (s, 3H). MS (MH⁺) 204.

c) [4-(4-Methoxy-phenyl)-oxazol-2-yl]-methanol

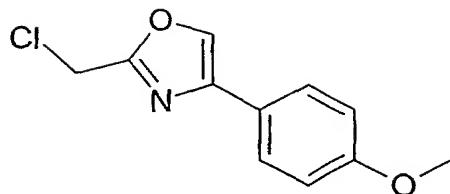


15

A solution of 4-(4-methoxy-phenyl)-oxazole-2-carbaldehyde (1.27 g, 6.23 mmol) in 50 mL ethanol: water (4 : 1) was treated with sodium borohydride (236 mg, 6.23 mmol) and stirred at room temperature for 30 minutes. The reaction was quenched with 2 mL acetone and evaporated. The remaining oil was dissolved in 75 mL methylene chloride and washed with 50 mL water. The organic layer was dried over sodium sulfate and evaporated and the remaining oil purified by chromatography on silica gel (elution with gradient hexane/ethyl acetate) to afford 1.17 g (92%) [4-(4-methoxy-phenyl)-oxazol-2-yl]-methanol as white crystals.

¹H NMR (CDCl₃, 300 MHz): δ 7.78 (s, 1H), 7.63 (d, 2H, J=9 Hz), 6.93 (d, 2H, J=9 Hz), 4.77 (s, 2H), 3.83 (s, 3H). MS (MH⁺) 206.

d) 2-Chloromethyl-4-(4-methoxy-phenyl)-oxazole

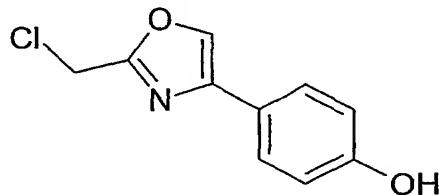


A solution of [4-(4-methoxy-phenyl)-oxazol-2-yl]-methanol (861 mg, 4.2 mmol) in 10 mL carbon tetrachloride was treated with triphenylphosphine (1.18 g, 4.49 mmol) and heated at 80°C for 7 hours. The solvent was evaporated and the remaining yellow solid purified by chromatography on silica gel (elution with gradient methylene chloride /ethanol) to afford 769 mg (82%) 2-chloromethyl-4-(4-methoxy-phenyl)-oxazole as yellow crystals.

¹H NMR (CDCl₃, 300 MHz): δ 7.83 (s, 1H), 7.65 (d, 2H, J=9 Hz), 6.94 (d, 2H, J=9 Hz), 4.65 (s, 2H), 3.85 (s, 3H). MS (MH⁺) 224.

10

e) 4-(2-Chloromethyl-oxazol-4-yl)-phenol

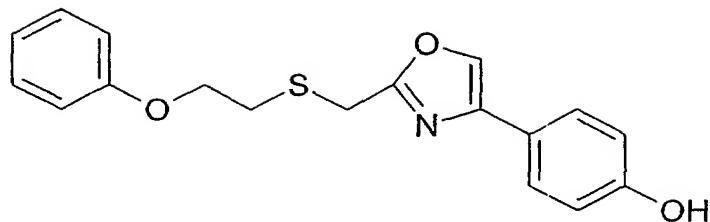


2-Chloromethyl-4-(4-methoxy-phenyl)-oxazole (753 mg, 3.37 mmol) was dissolved in 20 mL methylene chloride, cooled to -70°C and treated with 6.74 ml 1M boron tribromide solution in methylene chloride. Within 2 hours the reaction mixture was allowed to warm to room temperature and quenched with 15 mL saturated aqueous sodium bicarbonate solution. The organic layer was washed with 10 mL 2M hydrochloric acid, dried over sodium sulfate and evaporated to afford 682 mg (97%) 4-(2-chloromethyl-oxazol-4-yl)-phenol as a white solid.

¹H NMR (CDCl₃) δ 7.83 (s, 1H), 7.59 (d, 2H, J=9 Hz), 6.87 (d, 2H, J=9 Hz), 5.42 (br s, 1H), 4.65 (s, 2H). MS (MH⁺) 210.

f) 4-[2-(2-Phenoxy-ethylsulfanyl)methyl]-oxazol-4-yl]-phenol

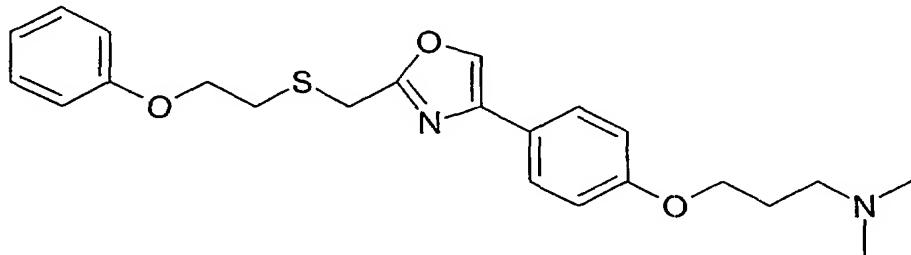
-340-



A solution of sodium hydride (82 mg, 3.42 mmol) in 3 mL ethanol was treated with 2-phenoxy-ethanethiol (502 mg, 3.25 mmol) in 2 mL ethanol at room temperature and stirred for 10 minutes. 4-(2-Chloromethyl-oxazol-4-yl)-phenol (682 mg, 3.25 mmol) was added and stirring was continued for 72 hours. The solvent was evaporated in vacuo and the remains were poured into 50 mL water. The precipitate was filtered, dried in vacuo to afford 1.02 g (96%) 4-[2-(2-phenoxyethanethiomethyl)-oxazol-4-yl]-phenol as a white solid.

¹H NMR (CDCl₃, 300 MHz): δ 7.77 (s, 1H), 7.75 (d, 2H, J=9 Hz), 7.26 (t, 2H, J=7 Hz), 6.98 – 6.82 (m, 5H), 4.16 (t, 2H, J=6 Hz), 3.93 (s, 2H), 3.03 (t, 2H, J=6 Hz). MS (MH⁺) 328.

g) Dimethyl-(3-{4-[2-(2-phenoxyethanethiomethyl)-oxazol-4-yl]-phenoxy}-propyl)-amine



¹H NMR (CDCl₃, 300 MHz): δ 7.77 (s, 1H), 7.75 (d, 2H, J=9 Hz), 7.26 (t, 2H, J=7 Hz), 6.98 – 6.82 (m, 5H), 4.16 (t, 2H, J=6 Hz), 3.93 (s, 2H), 3.03 (t, 2H, J=6 Hz). MS (MH⁺) 328.

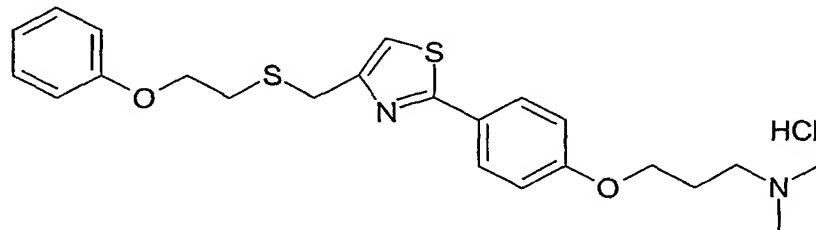
A suspension of 4-[2-(2-phenoxyethanethiomethyl)-oxazol-4-yl]-phenol (1.00 g, 3.05 mmol), dimethyl 3-chloro-propyl-amine hydrochloride (507 mg, 3.21 mmol), and potassium carbonate (929 mg, 6.72 mmol) in dimethylformamide (20 mL) was heated at 80°C for 24 hours. The solvent was removed in vacuo and the remains partitioned between water and methylene chloride. The organic layer was dried over sodium sulfate and evaporated. The remaining oil was purified by chromatography on silica gel (elution with gradient methylene chloride/ethanol containing 10% ammonia) to afford 765 mg (61

(%) of dimethyl-(3-{4-[2-(2-phenoxy-ethylsulfanyl)methyl]-oxazol-4-yl}-phenoxy)-propyl)-amine as white solid.

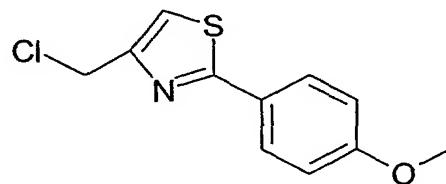
¹H NMR (CDCl₃, 300 MHz): δ 7.77 (s, 1H), 7.62 (d, 2H, J=9 Hz), 7.26 (t, 2H, J=7 Hz), 6.97 – 6.86 (m, 5H), 4.17 (t, 2H, J=7 Hz), 4.04 (t, 2H, J=7 Hz), 3.93 (s, 2H), 5 3.04 (t, 2H, J=7 Hz), 2.46 (t, 2H, J=7 Hz), 2.27 (s, 6H), 2.02 – 1.92 (m, 2H). MS (MH⁺) 413.

EXAMPLE 171

Preparation of Dimethyl-(3-{4-[2-(2-phenoxy-ethylsulfanyl)methyl]-thiazol-2-yl}-phenoxy)-propyl)-amine Hydrochloride



a) 4-Chloromethyl-2-(4-methoxy-phenyl)-thiazole

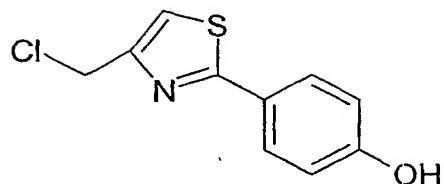


A solution of 4-methoxy-thiobenzamide (1.90 g, 11.33 mmol) and 1,3-dichloro acetone (2.8 g, 22.6 mmol) in 20 mL dimethylformamide was warmed to 100°C for 2 h. The reaction mixture was allowed to cool to room temperature and poured into 30 g of ice/water. The resulting precipitate was filtered and dried in vacuo to afford 1.60 g (59%) 4-chloromethyl-2-(4-methoxy-phenyl)-thiazole as a white solid.

¹H NMR (CDCl₃, 300 MHz): δ 7.88 (d, 2H, J=9 Hz), 7.23 (s, 1H), 6.95 (d, 2H, J=9 Hz), 4.72 (s, 2H), 3.83 (s, 3H). MS (MH⁺) 240.

b) 4-(4-Chloromethyl-thiazol-2-yl)-phenol

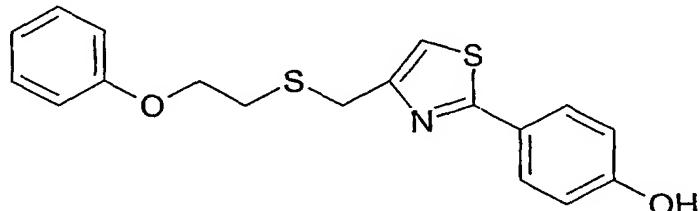
-342-



4-Chloromethyl-2-(4-methoxy-phenyl)-thiazole (1.0 g, 4.17 mmol) was dissolved in 20 mL methylene chloride, cooled to -70°C and treated with 8.34 mL 1M boron tribromide solution in methylene chloride. Within 2 hours the reaction mixture was 5 allowed to warm to room temperature and quenched with 15 mL saturated aqueous sodium bicarbonate solution. The organic layer was washed with 10 mL 2M hydrochloric acid, dried over sodium sulfate and evaporated. The solid was stirred with 5 mL methylene chloride. The remaining solid was dried in vacuo to afford 795 mg (85%) 4-(4-chloromethyl-thiazol-2-yl)-phenol as a white solid.

10 ¹H NMR (DMSO-D₆, 300 MHz): δ 9.80 (br s, 1H), 7.77 (d, 2H, J=9 Hz), 7.67 (s, 1H), 6.87 (d, 2H, J=9 Hz), 4.83 (s, 2H). MS (MH⁺) 226.

c) 4-[4-(2-Phenoxy-ethylsulfanyl)methyl]-thiazol-2-yl]-phenol



15

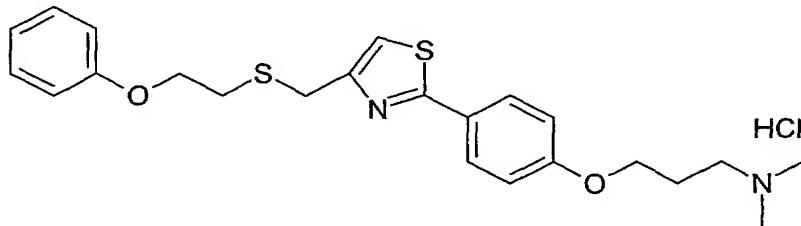
-343-

A solution of sodium hydride (80 mg, 3.34 mmol) in 5 mL ethanol was treated with 2-phenoxy-ethanethiol (490 mg, 3.18 mmol) in 2 mL ethanol at room temperature and stirred for 10 minutes. 4-(4-chloromethyl-thiazol-2-yl)-phenol (790 mg, 3.18 mmol) was added and stirring was continued for 16 hours. The solvent was evaporated in vacuo and the remains were poured into 50 mL water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and evaporated. The remaining oil was purified by chromatography on silica gel (elution with gradient methylene chloride/ethanol containing 10% ammonia) to afford 767 mg (70%) 4-[4-(2-phenoxy-ethylsulfanylmethyl)-thiazol-2-yl]-phenol as a white solid.

¹⁰ ¹H NMR (CDCl₃, 300 MHz): δ 7.80 (d, 2H, J=8 Hz), 7.26 (t, 2H, J=9 Hz), 7.07 (s, 1H), 6.98 – 6.80 (m, 5H), 5.69 (s, 1H), 4.18 (t, 2H, J=7 Hz), 3.99 (s, 2H), 2.96 (t, 2H, J=7 Hz).

MS (MH⁺) 344.

¹⁵ d) Dimethyl-(3-{4-[4-(2-phenoxy-ethylsulfanylmethyl)-thiazol-2-yl]-phenoxy}-propyl)-amine Hydrochloride



A suspension of 4-[4-(2-phenoxy-ethylsulfanylmethyl)-thiazol-2-yl]-phenol (751 mg, 2.19 mmol), dimethyl 3-chloro-propyl-amine hydrochloride (363 mg, 2.30 mmol), and potassium carbonate (665 mg, 4.81 mmol) in dimethylformamide (15 mL) was heated at 80°C for 14 hours. The solvent was removed in vacuo and the remains partitioned between water and methylene chloride. The organic layer was dried over sodium sulfate and evaporated. The remaining oil was purified by chromatography on silica gel (elution with gradient methylene chloride/ethanol containing 10% ammonia) to afford a white solid. The solid was dissolved in 10 mL dioxane and treated with 0.5 mL 4M HCl in dioxane and stirred for 10 minutes. Ether was added and the precipitation filtered and dried in vacuo to afford 546 mg (54%) of dimethyl-(3-{4-[4-(2-phenoxy-ethylsulfanylmethyl)-thiazol-2-yl]-phenoxy}-propyl)-amine as a white solid.

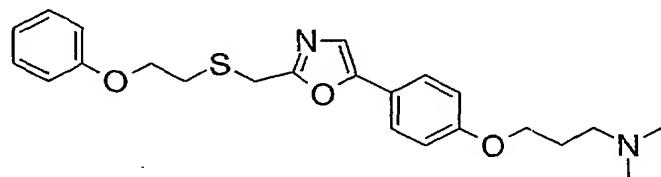
-344-

¹H NMR (DMSO-D₆, 300 MHz): δ 10.49 (br s, 1H), 7.86 (d, 2H, J=9 Hz), 7.46 (s, 1H), 7.27 (t, 2H, J=8 Hz), 7.04 (d, 2H, J=9 Hz), 6.97 – 6.89 (m, 3H), 4.22 – 3.98 (m, 6H), 3.97 (s, 2H), 3.26 – 3.17 (m, 2H), 2.94 (t, 2H, J=7 Hz), 2.79 (s, 3H), 2.77 (s, 3H), 2.23 – 2.11 (m, 2H). MS (MH⁺) 429.

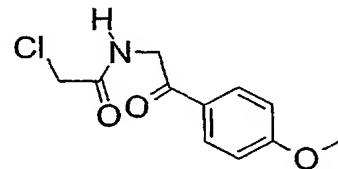
5

EXAMPLE 172

Dimethyl-(3-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenoxy}-propyl)-amine



10 a) 2-Chloro-N-[2-(4-methoxy-phenyl)-2-oxo-ethyl]-acetamide



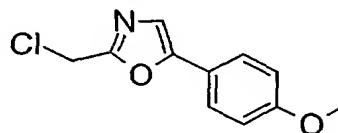
6.30 g (31 mmol) ω-amino-4-methoxy acetophenone hydrochloride was suspended in 70 mL methylene chloride and treated with 8.6 mL (62 mmol) triethylamine.

2.46 ml (31 mmol) of chloro acetylchloride was added drop wise under slight cooling

15 (~10°C). After complete addition the reaction mixture was stirred at room temperature for 24h. The reaction was quenched with water (100 mL) and the organic layer was dried over sodium sulfate and evaporated to yield 7.45 g (100%) 2-chloro-N-[2-(4-methoxy-phenyl)-2-oxo-ethyl]-acetamide.

20 ¹H NMR (CDCl₃, 300 MHz): δ 7.96 (d, 2H, J=7 Hz), 7.68 (br s, 1H), 6.98 (d, 2H, J=7 Hz), 4.73 (d, 2H, J=4 Hz), 4.13 (s, 2H), 3.89 (s, 3H).

b) 2-Chloromethyl-5-(4-methoxy-phenyl)-oxazole



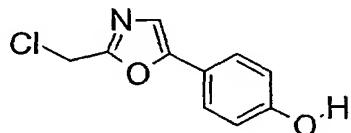
-345-

1.7 g (7 mmol) of 2-chloro-N-[2-(4-methoxy-phenyl)-2-oxo-ethyl]-acetamide was treated with 20 ml of phosphorous oxychloride and stirred for 2h at 100°C . The dark mixture was poured into water cautiously in portions. The temperature was held below 40°C by addition of ice. After being basification with conc. aqueous ammonia the mixture was extracted with tert.-butyl methylether. The organic layer was dried over sodium sulfate and evaporated to yield 1.5 g (96%) of 2-chloromethyl-5-(4-methoxy-phenyl)-oxazole.

¹H NMR (CDCl₃, 300 MHz): δ 7.58 (d, 2H, J=9 Hz), 7.19 (s, 1H), 6.95 (d, 2H, J=9 Hz), 4.66 (s, 2H), 3.85 (s, 3H).

10

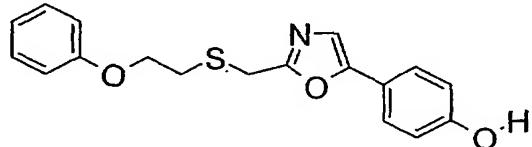
c) 4-(2-Chloromethyl-oxazol-5-yl)-phenol



1.4 g (6.2 mmol) of 2-chloromethyl-5-(4-methoxy-phenyl)-oxazole were dissolved in 25 mL methylene chloride, cooled to -70°C, and treated dropwise with 12.4 mL of a borone tribromide solution (1M in methylene chloride). After complete addition the reaction mixture was allowed to warm to room temperature. The mixture was poured into ice/water, basified with saturated aqueous sodium carbonate and acidified with aqueous 2M HCl solution. After extraction with methylene chloride, drying over sodium sulfate and evaporation, the crude product was dissolved in 5mL chloroform filtered and dried to yield 0.79 g (61%) 4-(2-chloromethyl-oxazol-5-yl)-phenol.

¹H NMR (DMSO-d₆, 300 MHz): δ 9.86 (br s, 1H), 7.54 (d, 2H, J=9 Hz), 7.47 (s, 1H), 6.86 (d, 2H, J=9 Hz), 4.91 (s, 2H).

d) 4-[2-(2-Phenoxy-ethanethiomethyl)-oxazol-5-yl]-phenol



25

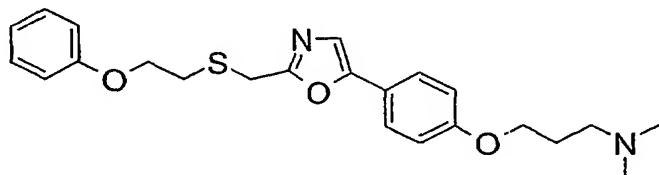
0.54 g (3.5 mmol) of 2-phenoxy-ethanethiol was dissolved in 8 ml of ethanol and treated with 1.75 mL (3.5 mmol) of 2M ethanolic sodium ethoxide solution. After stirring

-346-

at room temperature for 10 minutes 0.78 g (3.7 mmol) of 4-(2-chloromethyl-oxazol-5-yl)-phenol was added. Stirring at room temperature was continued for 20 hours. The solvent was evaporated and the residue was treated with 100 mL water and 100 mL ethyl acetate. The organic layer was dried over sodium sulfate and evaporated. The remaining oil was 5 purified by chromatography on silica gel (elution with gradient methylene chloride/ethanol) to afford 0.4 g (35%) 4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenol.

¹H NMR (DMSO-d₆, 300 MHz): δ 9.78 (s, 1H), 7.48 (d, 2H, J=8 Hz), 7.36 (s, 1H), 7.27 (t, 3H, J=8 Hz), 6.97 – 6.90 (m, 3H), 6.83 (d, 2H, J=8 Hz), 4.16 (t, 2H, J=6 Hz), 10 4.02 (s, 2H), 2.99 (t, 2H, J=6 Hz). MS (MH⁺) 328.

e) Dimethyl-(3-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenoxy}-propyl)-amine



15

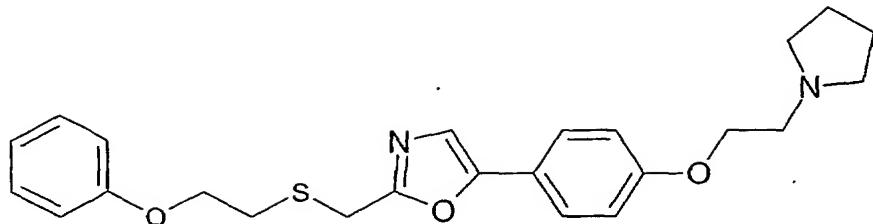
0.39 g (1.2 mmol) of 4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenol, 0.28 g (1.8 mmol) of 3-dimethylaminopropyl chloride hydrochloride, and 0.5 g (3.6 mmol) of potassium carbonate were dissolved in 10 mL dimethylformamide and heated to 80°C for 65 hours. The reaction mixture was poured into 100 mL water and was extracted 20 with tertiarybutyl methylether. The organic layer was dried over sodium sulfate and evaporated. The remaining oil was purified by HPLC to afford 70 mg (14 %) dimethyl-(3-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenoxy}-propyl)-amine.

¹H NMR (CDCl₃, 300 MHz): δ 7.53 (d, 2H, J=9 Hz), 7.30 – 7.22 (m, 2H), 7.12 (s, 1H), 6.98 – 6.85 (m, 5H), 4.17 (t, 2H, J=7 Hz), 4.05 (t, 2H, J=7 Hz), 3.94 (s, 2H), 3.04 (t, 2H, J=7 Hz), 2.47 (t, 2H, J=7 Hz), 2.27 (s, 6H), 2.03 – 1.92 (m, 2H). MS (MH⁺) 413.

Example 173

2-(2-Phenoxy-ethylsulfanylmethyl)-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-oxazole

-347-

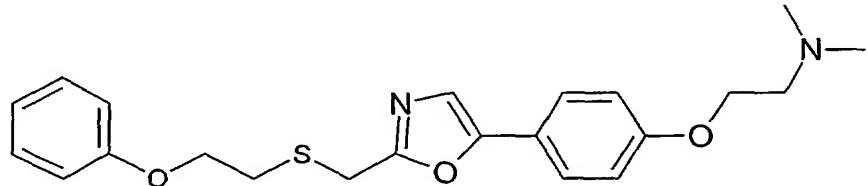


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 172 e, from 300 mg (0.92 mmol) 4-[2-(2-phenoxyethylsulfanylmethyl)-oxazol-5-yl]-phenol, 164 mg (0.962 mmol) N-(2-chloro-ethyl)-5 pyrrolidine hydrochloride, and 278 mg (2.015 mmol) potassium carbonate in 6 mL DMF. Yield: 209 mg (53%).

¹H NMR (CDCl₃, 300 MHz): δ 7.53 (d, 2H, J=9 Hz), 7.30 – 7.22 (m, 2H), 7.12 (s, 1H), 6.98 – 6.87 (m, 5H), 4.17 (t, 2H, J=7 Hz), 4.14 (t, 2H, J=7 Hz), 3.94 (s, 2H), 3.04 (t, 2H, J=7 Hz), 2.96 – 2.88 (m, 2H), 2.68 – 2.61 (m, 4H), 1.86 – 1.78 (m, 4H). MS (MH⁺) 10 425.

Example 174

Dimethyl-(2-{4-[2-(2-phenoxyethylsulfanylmethyl)-oxazol-5-yl]-phenoxy}-ethyl)-amine



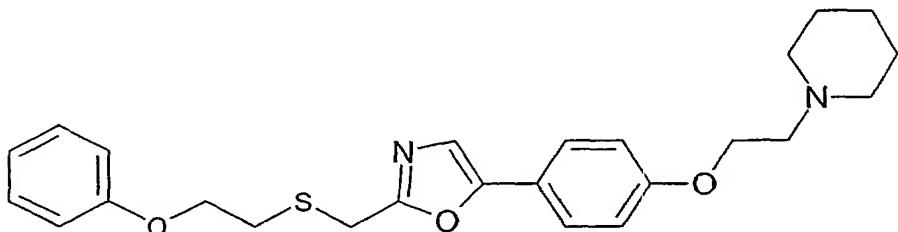
15 The above compound was prepared in a manner similar to that exemplified for the preparation of Example 172 e, from 455 mg (1.39 mmol) of 4-[2-(2-phenoxyethylsulfanylmethyl)-oxazol-5-yl]-phenol, 210 mg (1.46 mmol) (2-chloro-ethyl)-dimethylamine hydrochloride, and 423 mg (3.06 mmol) of potassium carbonate in 9 mL DMF. Yield: 304 mg (55%).

20 ¹H NMR (CDCl₃, 300 MHz): δ 7.53 (d, 2H, J=9 Hz), 7.29 – 7.23 (m, 2H), 7.12 (s, 1H), 6.98 – 6.87 (m, 5H), 4.17 (t, 2H, J=6 Hz), 4.10 (t, 2H, J=6 Hz), 3.94 (s, 2H), 3.04 (t, 2H, J=6 Hz), 2.75 (t, 2H, J=6 Hz), 2.35 (s, 6H). MS (MH⁺) 399.

Example 175

-348-

1-(2-{4-[2-(2-Phenoxy-ethylsulfanyl)methyl]-oxazol-5-yl}-phenoxy)-ethyl-piperidine

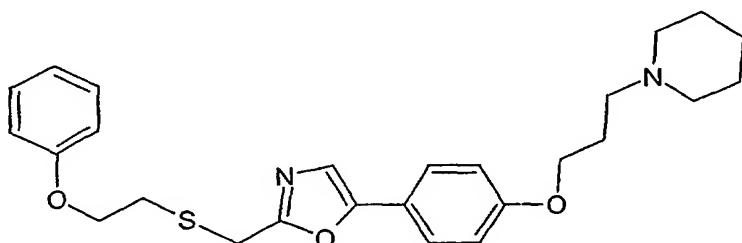


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 172 e, from 455 mg (1.39 mmol) 4-[2-(2-phenoxy-ethylsulfanyl)methyl]-oxazol-5-yl]-phenol, 269 mg (1.46 mmol), N-(2-chloro-ethyl)-piperidine hydrochloride, and 423 mg (3.06 mmol) of potassium carbonate in 9 mL DMF. Yield: 414 mg (68%).

¹H NMR (CDCl₃, 300 MHz): δ 7.53 (d, 2H, J=9 Hz), 7.30 – 7.22 (m, 2H), 7.12 (s, 1H), 6.98 – 6.87 (m, 5H), 4.17 (t, 2H, J=7 Hz), 4.14 (t, 2H, J=7 Hz), 3.94 (s, 2H), 3.04 (t, 2H, J=6 Hz), 2.79 (t, 2H, J=6 Hz), 2.56 – 2.48 (m, 4H), 1.67 – 1.57 (m, 4H), 1.50 – 1.41 (m, 2H). MS (MH⁺) 439.

Example 176

1-(3-{4-[2-(2-Phenoxy-ethylsulfanyl)methyl]-oxazol-5-yl}-phenoxy)-propyl-piperidine



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 172 e, from 455 mg (1.39 mmol) 4-[2-(2-phenoxy-ethylsulfanyl)methyl]-oxazol-5-yl]-phenol, 289 mg (1.46 mmol) N-(3-chloro-propyl)-piperidine hydrochloride, and 423 mg (3.06 mmol) potassium carbonate in 9 mL DMF. Yield: 525 mg (83%).

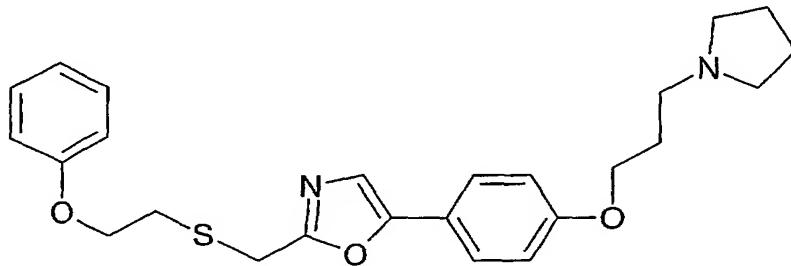
¹H NMR (CDCl₃, 300 MHz): δ 7.52 (d, 2H, J=9 Hz), 7.30 – 7.22 (m, 2H), 7.12 (s, 1H), 6.98 – 6.87 (m, 5H), 4.17 (t, 2H, J=6 Hz), 4.04 (t, 2H, J=6 Hz), 3.94 (s, 2H), 3.04 (t,

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2H, J=6 Hz), 2.52 – 2.37 (m, 6H), 2.05 – 1.93 (m, 2H), 1.66 – 1.55 (m, 4H), 1.50 – 1.40 (m, 2H). MS (MH⁺) 453.

Example 177

5 2-(2-Phenoxy-ethylsulfanylmethyl)-5-[4-(3-pyrrolidin-1-yl-propoxy)-phenyl]-oxazole

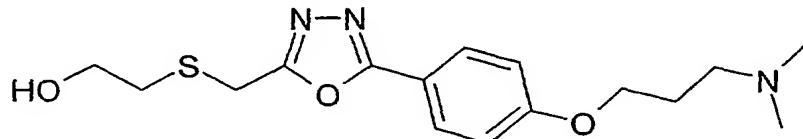


The above compound was prepared in a manner similar to that exemplified for the
10 preparation of Example 172 e, from 455 mg (1.39 mmol) 4-[2-(2-phenoxy-
ethylsulfanylmethyl)-oxazol-5-yl]-phenol, 269 mg (1.46 mmol) N-(3-chloro-propyl)-
pyrrolidine hydrochloride, and 423 mg (3.06 mmol) potassium carbonate in 9 mL DMF.
Yield : 470 mg (77%).

¹H NMR (CDCl₃, 300 MHz): δ 7.53 (d, 2H, J=9 Hz), 7.30 – 7.22 (m, 2H), 7.12 (s,
15 1H), 6.98 – 6.87 (m, 5H), 4.17 (t, 2H, J=6 Hz), 4.14 (t, 2H, J=6 Hz), 3.94 (s, 2H), 3.04 (t,
2H, J=7 Hz), 2.78 (t, 2H, J=7 Hz), 2.56 – 2.49 (m, 4H), 1.67 – 1.58 (m, 4H), 1.50 – 1.41 (m, 2H). MS (MH⁺) 439.

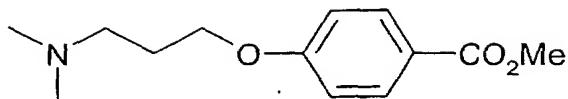
Example 178

20 Preparation of 2-(2-hydroxyethylthio)methyl-5-(4-[3-(dimethylamino)propoxy]-phenyl)-1,3,4-oxadiazole hydrochloride from methyl 4-hydroxy-benzoate



a) Methyl 4-[3-(dimethylamino)propoxy]-benzoate

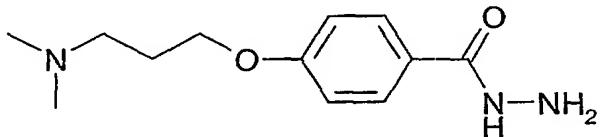
-350-



To a solution of 4-hydroxy benzoic acid methyl ester (50.0 g, 328.6 mmol), triphenyl phosphine (130.0 g, 493.5 mmol), and 3-dimethylamino-1-propanol (50.5 g, 57 ml, 493.5 mmol) in 1000 mL of dry THF was added dropwise isopropyl azo dicarboxylate 5 at 0 °C. After completed addition the temperature was brought to ambient temperature and the mixture was stirred for 16 h. The mixture was evaporated. It was then dissolved in ethyl acetate and extracted with 2N aqueous HCl. The aqueous phase was made alkaline with solid sodium hydroxide pellets and extracted with ethyl acetate (3 times). The collected organic phases were dried with sodium sulphate and evaporated. The crude 10 material (75 g, 96%) was used directly in the next step.

¹H NMR (DMSO-d₆) δ 7.95 (d, 2H, J=8 Hz), 7.00 (d, 2H, J=8 Hz), 4.13 (t, 2H, J=6 Hz), 3.83 (s, 3H), 2.32(t, 2H, J=6 Hz), 2.13 (s 6H), and 1.88 (quint., 2H, J=6 Hz), MS (FD) m/e 238.

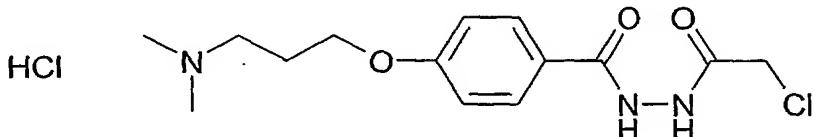
15 b) 4-[3-(dimethylamino)propoxy]-benzoic acid hydrazide



A solution of methyl 4-[3-(dimethylamino)propoxy]-benzoate (108.0 g, 457.0 mmol), in 443 ml (458 g, 9.14 M) of neat hydrazine hydrate was subdivided into ten 20 aliquots and each aliquot was heated in a Teflon bomb in a microwave oven ETHOS 1600 for 1 h to 120 °C. After TLC indicated complete conversion the reaction mixture was poured in water and extracted with DCM. The collected organic phases were dried over sodium sulphate, filtered and evaporated. The residue was purified via column chromatography using a DCM/DCM-MeOH/ DCM-MeOH-ammonia gradient (100% to 25 90:10). Yield 32.7 g (42%).

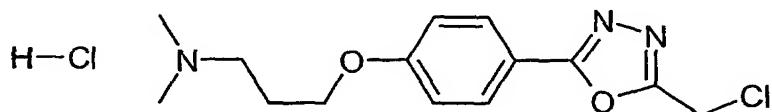
¹H NMR (DMSO-d₆) δ 9.58 (s, 1H, exch.), 7.80 (d, 2H, J=8 Hz), 6.98 (d, 2H, J=8 Hz), 4.40 (s, 2H, br., exch.), 4.05 (t, 2H, J=6 Hz), 2.35(t, 2H, J=6 Hz), 2.15 (s 6H), and 1.88 (quint., 2H, J=6 Hz), MS (FD) m/e 238.

- c) 4-[3-(dimethylamino)propoxy]-benzoic acid 2-(chloroacetyl)hydrazide hydrochloride



Chloro acetylchloride (2.40 g, 1.68 ml, 21.07 mmol) was slowly added to a solution of 4-[3-(dimethylamino)propoxy]-benzoic acid hydrazide (5.0 g, 21.07 mmol) in 50 ml DCM. After stirring overnight at ambient temperature TLC showed incomplete conversion. After successive addition of chloro acetyl chloride (0.17 ml, additional stirring for 2h, 0.5 ml additional stirring for 1 h) TLC showed almost complete conversion. The mixture was diluted with 50 ml MTBE and the colorless precipitate thus formed was filtered off and dried in a vacuum oven at 40 °C for 1 h. 6.7 g (91 %) of colorless crystals. The material was used in the next step without purification.

- d) 2-Chloromethyl-5-(4-[3-(dimethylamino)propoxy]-phenyl)-1,3,4-oxadiazole hydrochloride



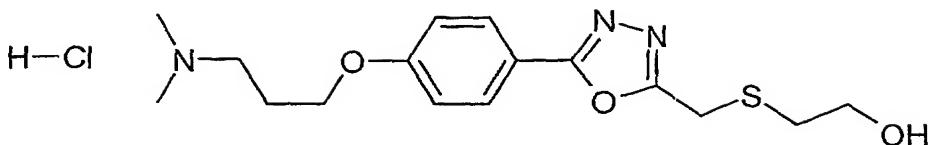
4-[3-(dimethylamino)propoxy]-benzoic acid 2-(chloroacetyl)hydrazide (6.7 g, 19.13 mmol) was added to 34 ml of phosphoryl chloride POCl_3 and the mixture was stirred at 95 °C overnight. The mixture was diluted with DCM and evaporated to dryness. The residue was repeatedly triturated with toluene and evaporated to remove remaining traces of POCl_3 and HCl. The colorless residue was sufficiently pure for the next step.

^1H NMR (DMSO-d₆) δ 10.58 (s, 1H, exch.), 7.98 (d, 2H, J=8 Hz), 7.20 (d, 2H, J=8 Hz), 5.12 (s, 2H), 4.18 (t, 2H, J=6 Hz), 3.20 (t, 2H, J=6 Hz), 2.80 (d, 6H, J=4 Hz), and 2.20 (quint., 2H, J=6 Hz). MS (FD) m/e 296.1.

e)

- 2-(2-hydroxyethylthio)methyl-5-(4-[3-(dimethylamino)propoxy]-phenyl)-1,3,4-oxadiazole hydrochloride

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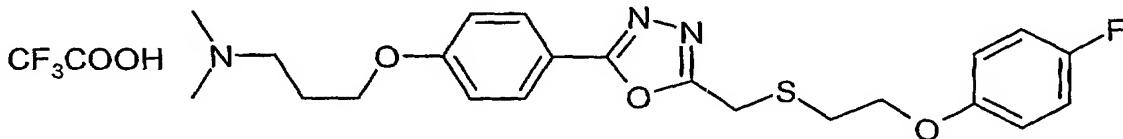


To a solution of sodium ethylate in ethanol, prepared by adding sodium hydride (60% dispersion, 2.1 g, 51.96 mmol) to 90 ml of absolute ethanol was added 2-mercaptopropanoic acid (4.1 g, 51.96 mmol, 3.7 ml). The mixture was stirred at room temperature for 30 min. Then 2-chloromethyl-5-(4-[3-(dimethylamino)propoxy]-phenyl)-1,3,4-oxadiazole hydrochloride (8.6 g, 25.98 mmol) was added as a solid. After 2 h stirring at ambient temperature the mixture was evaporated. The residue was suspended in DCM (dichloromethane) and extracted with aqueous sodium bicarbonate. The organic phase was dried over sodium sulphate and evaporated the residue was purified via flash chromatography on silica gel using DCM-DCM/ethanolic ammonia gradient (100% to 90% DCM) yielding 4.8 g (49%) of pure compound.

¹H NMR (DMSO-d₆) δ 7.90 (d, 2H, J=8 Hz), 7.12 (d, 2H, J=8 Hz), 4.88 (t, 1H, exch.), 4.10 (m, 2H), 4.10 (s, 2H), 3.57 (q, 2H), 2.72 (t 2H, J=4 Hz), 2.36 (t, 2H, J=4 Hz), 2.18 (s, 6H) and 1.88 (quint. 2H, J=4 Hz). MS (FD) m/e 338.1.

15

f) Dimethyl-(3-{4-[5-(2-(4-fluorophenoxy-ethylsulfanyl)methyl)-1,3,4-oxadiazol-2-yl]-phenoxy}-propyl)-amine.



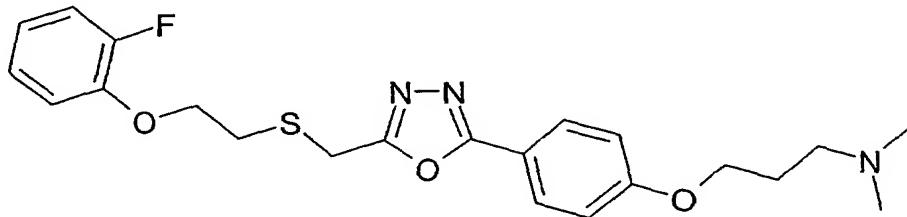
To a mixture of 2-(2-hydroxyethylthio)methyl-5-(4-[3-(dimethylamino)propoxy]-phenyl)-1,3,4-oxadiazole hydrochloride (0.200 g, 0.592 mmol), 4-fluorophenol (0.100 mg, 0.888 mmol) triphenyl phosphine polystyrene resin (0.888 g, 0.888 mmol, 1 meq./g) in 6 ml DCM was added diisopropyl azodicarboxylate (0.180 g, 176 μl, 0.888 mmol) and stirred at ambient temperature for 12 h. The mixture was evaporated and redissolved in methanol. The solution was purified via a SCX-cartridge using 20 ml methanol to remove impurities. The compound was eluted with methanolic ammonia. The residue (206 mg) was finally purified via prep. HPLC (RP-18) using acetonitrile/water/0.1% TFA gradient yielding 44 mg (17%) of the desired compound

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¹H NMR (DMSO-d₆) δ 9.50 (s, br, exch) 7.89 (m, 2H), 7.05 (m, 6H), 4.25 (s, 2H), 4.10 (m, 2H), 3.90 (m, br 2H), 3.23 (m, 2H), 3.05 (q, 2H), 2.80 (2s, 6H), and 2.12 (m, 2H). MS (FD) m/e 432.1.

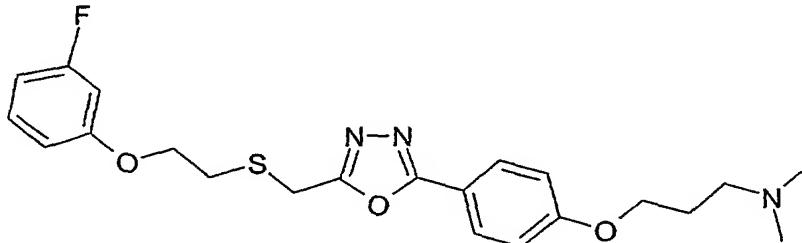
5 The following compounds were prepared using the protocol described above, using 2-(2-hydroxyethylthio)methyl-5-(4-[3-(dimethylamino)propoxy]-phenyl)-1,3,4-oxadiazole and the appropriate substituted phenol. After prep. HPLC the appropriate fractions were collected, evaporated and redissolved in methanol. Filtration of the methanolic solution of the trifluoroacetate salts of the desired compounds through SCX 10 cartridges yielded the free bases of the desired compounds:

Example 179



15 ¹H NMR (CDCl₃) δ 7.97 (d, 2H, J=8 Hz), 7.00 (m, 4H), 6.98(d, 2H, J=8 Hz), 6.65 (m, 3H), 4.28 (t, 2H), 4.11 (s, 2H), 4.10 (t, 2H), 3.10 (t, 2H), 2.40 (t, 2H), 2.30 (s, 6H), and 2.00 (quint., 2H). MS (FD) m/e 432.1.

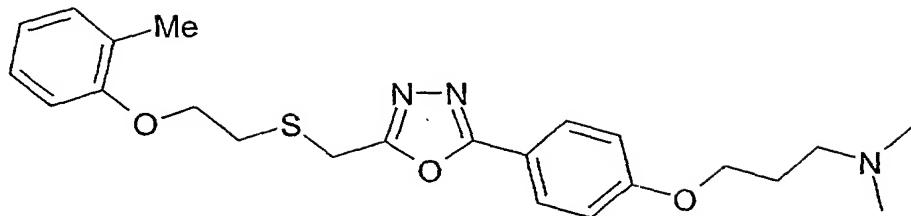
Example 180



20 ¹H NMR (CDCl₃) δ 7.95 (d, 2H, J=8 Hz), 7.20 (m, 1H), 6.98(d, 2H, J=8 Hz), 6.65 (m, 3H), 4.20 (t, 2H), 4.12 (t, 2H), 4.03 (s, 2H), 3.05 (t, 2H), 2.45 (t, 2H), 2.25 (s, 6H), and 2.00 (quint., 2H). MS (FD) m/e 432.1.

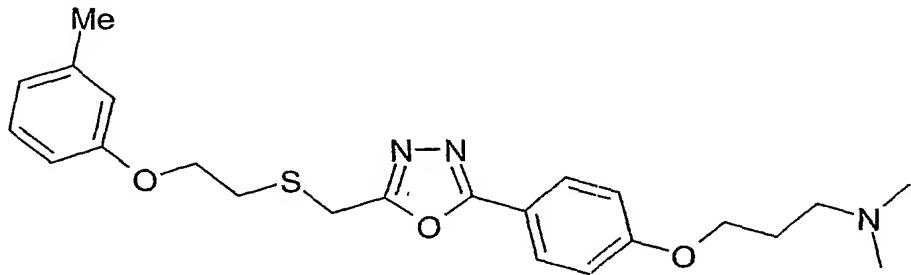
-354-

Example 181



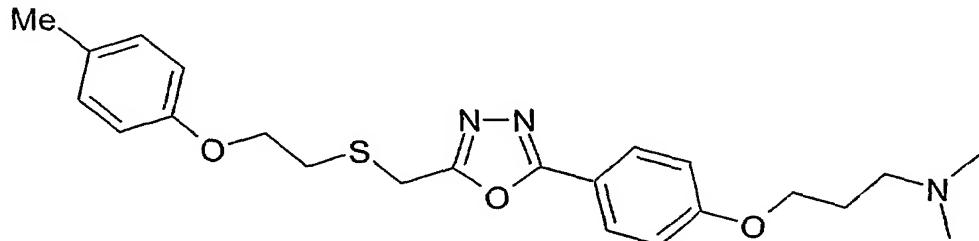
¹H NMR (CDCl₃) δ 7.95 (d, 2H, J=8 Hz), 7.12 (d, 2H, J=8 Hz), 7.00(d, 2H, J=8 Hz), 6.85 (m, 2H), 4.25 (t, 2H), 4.13 (t, 2H), 4.08 (s, 2H), 3.10 (t, 2H), 2.50 (t, 2H), 2.28 (s, 6H), 2.23 (s, 3H), and 1.98 (quint., 2H). MS (FD) m/e 428.1.

Example 182



¹H NMR (CDCl₃) δ 7.95 (d, 2H, J=8 Hz), 7.15 (t, 1H, J=8 Hz), 7.00(d, 2H, J=8 Hz), 6.75 (m, 2H), 4.20 (t, 2H), 4.10 (t, 2H), 4.05 (s, 2H), 3.05 (t, 2H), 2.45 (t, 2H), 2.33 (s, 3H), 2.30 (s, 6H), and 1.98 (quint., 2H). MS (FD) m/e 428.1.

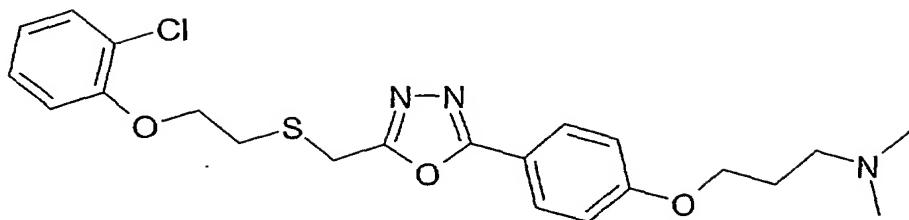
Example 183



¹H NMR (CDCl₃) δ 7.93 (d, 2H, J=8 Hz), 7.08 (d, 1H, J=8 Hz), 7.20 (t, 1H), 7.00 (d, 2H, J=8 Hz), 6.80 (d, 2H, J=8 Hz), 4.18 (t, 2H), 4.10 (t, 2H), 4.05 (s, 2H), 3.07 (t, 2H), 2.50 (t, 2H), 2.27 (s, 6H), 2.26 (s, 3H), and 2.00 (quint., 2H). MS (FD) m/e 428.2.

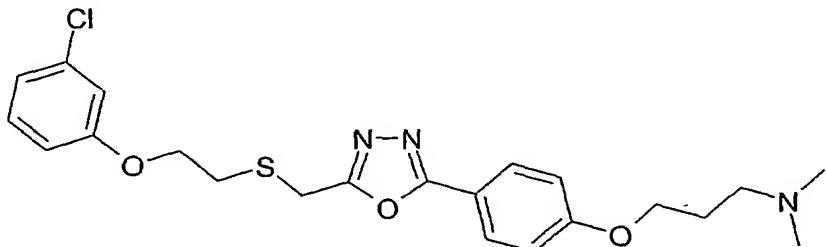
-355-

Example 184



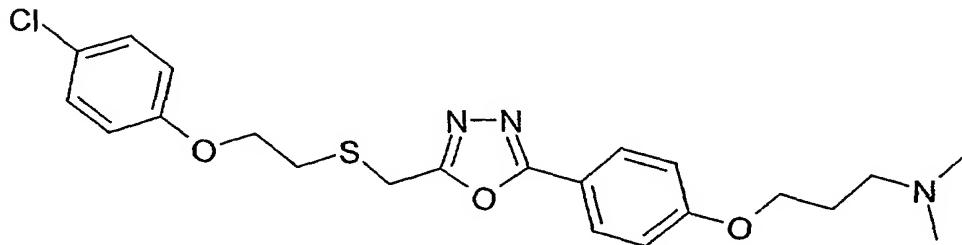
¹H NMR (CDCl₃) δ 7.93 (d, 2H, J=8 Hz), 7.33 (d, 1H, J=8 Hz), 7.20 (t, 1H), 7.00 (d, 2H, J=8 Hz), 6.90 (d, 2H, J=8 Hz), 6.70 (d, 1H), 4.30 (t, 2H), 4.15 (s, 2H), 4.10 (t, 2H), 3.10 (t, 2H), 2.50 (t, 2H), 2.27 (s, 6H), and 2.00 (quint., 2H). MS (FD) m/e 448.1.

Example 185



¹H NMR (CDCl₃) δ 7.88 (d, 2H, J=8 Hz), 7.11 (t, 1H, J=8 Hz), 6.90 (d, 2H, J=8 Hz), 6.75 (m, 2H), 6.70 (d, 1H), 4.10 (t, 2H), 4.02 (t, 2H), 3.98 (s, 2H), 3.01 (t, 2H), 2.40 (t, 2H), 2.21 (s, 6H), and 1.90 (quint., 2H). MS (FD) m/e 448.0.

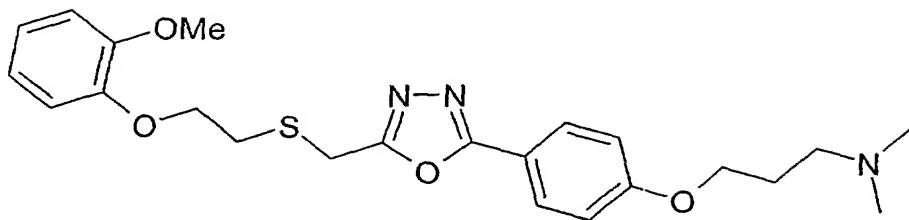
Example 186



¹H NMR (MeOD) δ 7.39 (d, 2H, J=8 Hz), 7.20 (d, 2H, J=9 Hz), 7.02 (d, 2H, J=8 Hz), 6.83 (d, 2H, J=9 Hz), 4.20 (t, 2H), 4.10 (t, 2H), 4.08 (s, 2H), 3.07 (t, 2H), 2.55 (t, 2H), 2.35 (s, 6H), and 2.05 (quint., 2H). MS (FD) m/e 448.1.

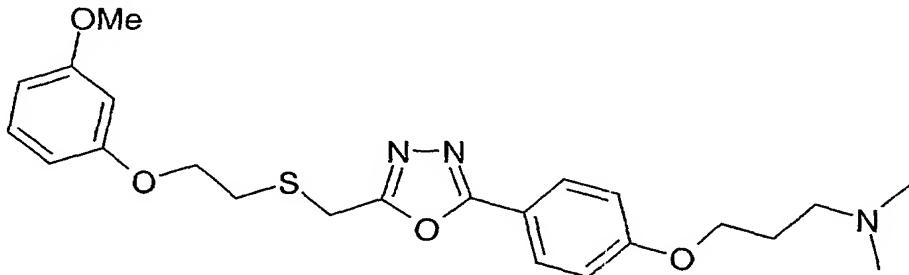
-356-

Example 187



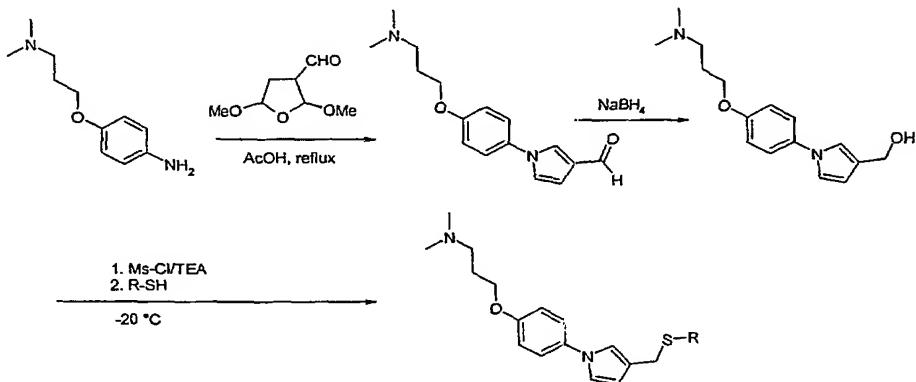
¹H NMR (CDCl₃) δ 7.95 (d, 2H, J=8Hz), 7.00 (d, 2H, J=8Hz), 6.90 (m, 4H), 4.20 (t, 2H), 4.10 (t, 2H), 4.05 (s, 2H) 3.78 (s, 3H), 3.07 (t, 2H), 2.45 (t, 2H), 2.25 (s, 6H), and 5 1.98 (m, 2H). MS (FD) m/e 444.2.

Example 188



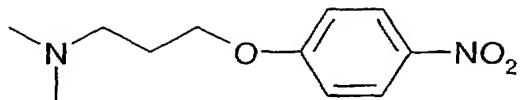
¹H NMR (CDCl₃) 7.95 (m, 2H), 7.15 (t, 1H, J=8Hz), 7.00 (m, 2H), 6.42 (m, 3H), 10 4.20 (t, 2H), 4.05 (t, 2H), 4.05 (s, 2H) 3.78 (s, 3H), 3.05 (t, 2H), 2.45 (t, 2H), 2.25 (s, 6H), and 1.98 (m, 2H). MS (FD) m/e 444.2

Example 189



15

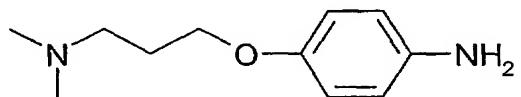
a) 4-[3-(dimethylamino)propoxy]-nitro benzene



To a suspension of 4-nitro phenol (30.0 g, 216 mmol), anhydrous potassium carbonate (86.7 g, 627 mmol), and potassium iodide (5.5 g, 33 mmol) in 360 ml of dry DMF was added finely ground 3-dimethylamino-1-propyl chloride hydrochloride (51.7 g, 327 mmol). The mixture was stirred at 80 °C for 4 days. Successively another portion of 3-dimethylamino-1-propyl chloride hydrochloride (15.81 g, 100 mmol) and anhydrous potassium carbonate (25.2 g, 200 mmol) was added and stirring at 80 °C was continued for 16 h. After cooling the mixture was diluted with 1.5 l water and extracted with MTBE (2 times 600 ml). The collected organic phases were dried with sodium sulphate and evaporated. The crude yellow oil (31.7 g, 65.6%) was sufficiently pure and used directly in the next step.

¹H NMR (CDCl₃) δ 8.19 (d, 2H, J=8 Hz), 6.96 (d, 2H, J=8 Hz), 4.13 (t, 2H, J=6 Hz), 2.48(t, 2H, J=6 Hz), 2.28 (s 6H), and 2.00 (quint., 2H, J=6 Hz), MS (FD) m/e 225.1.

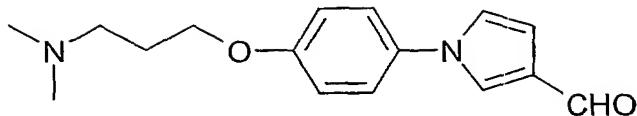
15 b) 4-[3-(dimethylamino)propoxy]-aniline



To a solution of 4-[3-(dimethylamino)propoxy]-nitro benzene (12 g, 54 mmol) in 65 ml of absolute ethanol was added 200 mg of Pd(OH)₂ on carbon (Pearlman's catalyst). The mixture was hydrogenated at atmospheric hydrogen pressure for 16 h. The mixture 20 was filtered over diatomeous earth and the filter cake rinsed with ethanol. The collected ethanolic filtrates were evaporated. The crude orange oil (10.38g, 99%) was sufficiently pure and used directly in the next step.

¹H NMR (CDCl₃) δ 6.83 (d, 2H, J=8 Hz), 6.72 (d, 2H, J=8 Hz), 3.83 (t, 2H, J=6 Hz), 3.40 (s, br, exch. 2H) 2.42(t, 2H, J=6 Hz), 2.25 (s 6H), and 1.91 (quint., 2H, J=6 Hz), MS (FD) m/e 195.0.

c) 1-[4-(3-dimethylaminopropoxy)-phenyl]-1H-pyrrole-3-carboxaldehyde



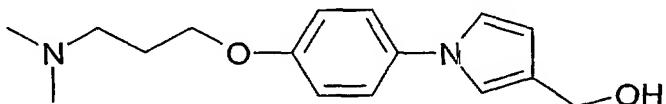
To a solution of 3-formyl-(2,5-dimethoxytetrahydrofuran) (7.5 g, 47 mmol) in 50 ml of glacial acetic acid was added 4-[3-(dimethylamino)propoxy]-aniline (9.8 g, 50 mmol). A slightly exothermic reaction occurred and the mixture darkened. The mixture
5 was stirred at 110 °C for 1 h and poured into 400 ml of crushed ice after cooling to ambient temperature. The aqueous phase was neutralized with solid sodium bicarbonate and exhaustively extracted with DCM.

The collected organic phases were dried over sodium sulphate and evaporated.
The crude product was purified via flash chromatography on silica gel using a DCM/
10 DCM-ethanolic ammonia gradient 100 to 95:5. A reddish-brown oil was obtained (4.23 g,
33%).

¹H NMR (CDCl₃) δ 9.84 (s, 1H), 7.58 (t, 2H, J=2 Hz), 7.32 (d, 2H, J=8 Hz), 7.00
15 (d, 2H, J=8 Hz), 7.00 (m, 1H), 6.77 (m, 1H), 4.08 (t, 2H, J=6 Hz), 2.48(t, 2H, J=6 Hz),
2.28 (s 6H), and 1.99 (quint., 2H, J=6 Hz). MS (FD) m/e 273.1.

15

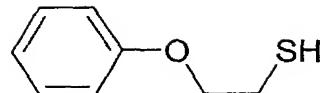
d) 1-[4-(3-dimethylaminopropoxy)phenyl]-1H-pyrrole-3-methanol



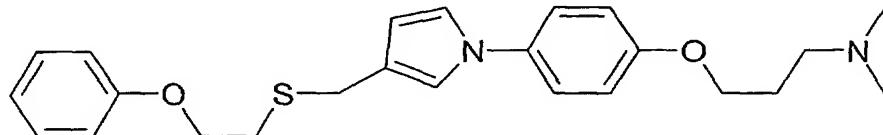
To a stirred solution of DIBAH (17.1 ml, 20% in toluene, 21.2 mmol) was added
1-[4-(3-dimethylaminopropoxy)-phenyl]-1H-pyrrole-3-carboxaldehyde (2.9 g, 10.6 mmol)
20 at 0 to 2°C. After stirring for 1 h at 0 °C the reaction was completed. Excess DIBAH was
quenched with 10 ml of toluene/methanol 1:1 under cooling. The gelatinous mixture was
solubilized with methanol and evaporated. The residue was extracted successively with
DCM and methanol and filtered off. The organic filtrate was evaporated yielding a dark
oil (3.0 g, 100%) which solidified in a freezer. According to HPLC the material was
approx. 80% pure and was used without further purification.
25

¹H NMR (CDCl₃) δ 7.20 (d, 2H, J=8 Hz), 7.32 (d, 2H, J=8 Hz), 7.00 (d, 2H, J=8
Hz), 6.90 (m, 4H), 4.55 (s, 2H), 3.95 (t, 2H, J=6 Hz), 2.40(t, 2H, J=6 Hz), 2.20 (s 6H),
1.90, (quint., 2H, J=6 Hz), and 1.70 (s, br, exch.1H). MS (FD) m/e 275.2.

2-Phenoxyethanethiol



The compound was prepared according to: J. Org. Chem. 1972, 37(10), 1532-37.



5

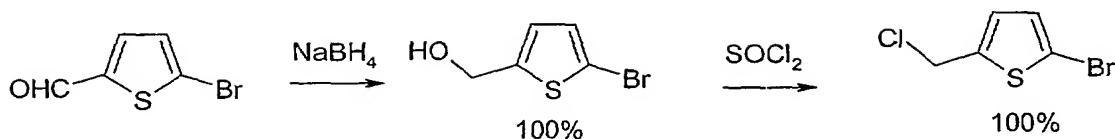
To a stirred solution of 1-[4-(3-dimethylaminopropoxy)phenyl]-1H-pyrrole-3-methanol (360 mg, 1.3 mmol) in 15 ml of dry THF was added triethyl amine (334 mg, 3.3 mmol) and 10 mg DMAP and the mixture was cooled to -8 °C. A solution of methane sulfonyl chloride (223 mg, 1.55 mmol) in 2 ml dry THF was added dropwise and the mixture was stirred for 30 min at -5 °C. TLC showed almost complete conversion. After stirring for additional 2.5 h at -5 to 0 °C the mixture was quenched with 60 % sodium hydride (62 mg, 1.55 mmol) and stirred for 15 min at 0 °C. In the meantime a solution of sodium 2-phenoxyethanethiolate was prepared from 2-phenoxy ethanethiol (401 mg, 2.6 mmol) and sodium hydride (60%, 104 mg, 2.6 mmol) in 2 ml dry THF. After 15 min of stirring the solution was cooled to 0 °C and slowly added to the solution of the mesylate. The mixture was stirred at 0° C for 30 min and then for 16 h at ambient temperature. The mixture was evaporated and the residue purified on an aluminum oxide (neutral) column. The main fraction was isolated as an orange oil (38 mg), which was 73 % pure according to HPLC. The crude product was further purified by prep. HPLC (RP-18 acetonitrile/water/0.1% TFA) yielding 24.8 mg of the desired product as the triflate salt (3.6 %).

¹H NMR (CDCl₃) δ 11.8 (s br. 1H), 7.26 (m, 4H,), 6.92 (m, 7H,), 6.30 (t, 1H, J=1 Hz), 4.10 (qu,qu, 4H), 3.88 (s, 2H), 3.30 (qu, 2H,), 2.90(s+m, 8H,), 2.28 (m, 2H). MS (FD) m/e 411.2.

25

2-Bromo-5-(chloromethyl)-thiophene

-360-



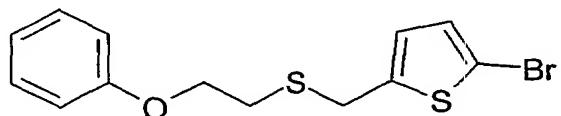
To a suspension of sodium borohydride (400 mg, 10.6 mmol) in 30 ml 2-propanol was added dropwise a solution of 5-bromothiophene-2-carboxaldehyde (2g, 10.45 mmol) in 5 ml 2-propanol at ambient temperature. After stirring for 1 h at ambient temperature 5 the mixture was carefully hydrolyzed by 2N aqueous hydrochloric acid under ice cooling. The pH value was adjusted to 3 to 4 and the solution was extracted with DCM. The organic phase was dried over sodium sulfate, filtered and evaporated. The residue (1.9 g) was sufficiently pure for the next step.

¹H NMR (CDCl₃) δ 6.91 (d, 1H, J=4 Hz), 6.75 (d, 1H, J=4 Hz), 4.75 (s, 2H,), 1.90 (s, br., exch.).

A solution of the foregoing 2-bromo-5-thiophene methanol (1.9 g, 10.45 mmol) and thionyl chloride (2.5 g) in 30 ml dry DCM was stirred at ambient temperature for 2 h. The solution was evaporated and the residue repeatedly re-dissolved in toluene and evaporated to remove traces of thionyl chloride. The crude residue (2.1 g) was directly used in the next step.

¹H NMR (CDCl₃) δ 6.92 (d, 1H, J=4 Hz), 6.83 (d, 1H, J=4 Hz), 4.70 (s, 2H). MS (FD) m/e 212.0.

20 2-Bromo-5-[(2-phenoxy)ethylthio)methyl]-thiophene



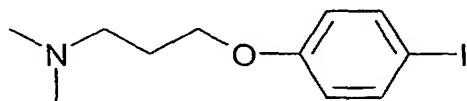
To a 2.5 N solution of sodium ethoxide (prepared from 120 mg, 5 mmol 60% sodium hydride and 20 ml of dry ethanol) was added dropwise 2-phenoxyethanethiol (770 mg, 5 mmol) and stirred for 30 min at ambient temperature. To this solution was added 2-
25 bromo-5-(chloromethyl)-thiophene (1000 mg, 5mM) dropwise and the mixture was stirred over night at ambient temperature. The mixture was carefully hydrolyzed with water and extracted with ethyl acetate. The organic phase was dried, filtered and

evaporated. The residue was purified via flash chromatography on silica gel using hexane/ethyl acetate 97.5:2.5 yielding 1.2 g (79%) of the desired compound.

¹H NMR (CDCl₃) δ 7.30 (m, 2H), 6.92 (m, 4H), 6.71 (d, 2H, J=3 Hz), 4.41 (t, 2H, J=6.5 Hz), 3.97 (s, 2H), 2.88 (t, 2H, J=6.5 Hz). MS (EI) m/e 328.

5

a) 4-[3-(dimethylamino)propoxy]-iodo benzene

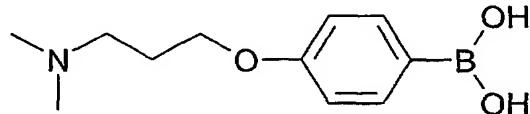


10 To a suspension of 4-iodo phenol (24.0 g, 110 mmol), anhydrous potassium carbonate (36.0 g, 260 mmol), and potassium iodide (2.2 g, 13 mmol) in 240 ml of dry 2-butanone was added finely ground 3-dimethylamino-1-propyl chloride hydrochloride (13.4 g, 110 mmol). The mixture was stirred under reflux for 48 h. The solvent was distilled off. The residue was dissolved in DCM and extracted with 2N aqueous NaOH twice. The organic phase was separated washed with water twice, dried and evaporated.

15 The crude oil (21.0 g) was purified via flash chromatography on silica gel using a DCM/ethanolic ammonia gradient (100 to 95:5) yielding 12.9 g of the desired compound sufficiently pure for the next step.

¹H NMR (CDCl₃) δ 7.55 (d, 2H, J=8 Hz), 6.70 (d, 2H, J=8 Hz), 4.00 (t, 2H, J=4 Hz), 2.45(t, 2H, J=4 Hz), 2.23 (s 6H), and 1.95 (quint., 2H, J=4 Hz). MS (FD) m/e 306.0.

[4-[3-(dimethylamino)propoxy]phenyl]boronic acid



25 To a solution of 4-[3-(dimethylamino)propoxy]-iodo benzene (1 g, 3.28 mmol) in abs. THF was added a solution of n-butyl lithium in hexane (2.5 ml, 1.6 M solution, 4 mmol) at -78 °C under vigorous stirring within 5 min. After stirring at -78 °C for 30 min a solution of trimethyl borate (433 µl, 3.94 mmol) in 10 ml abs. THF was added within 10

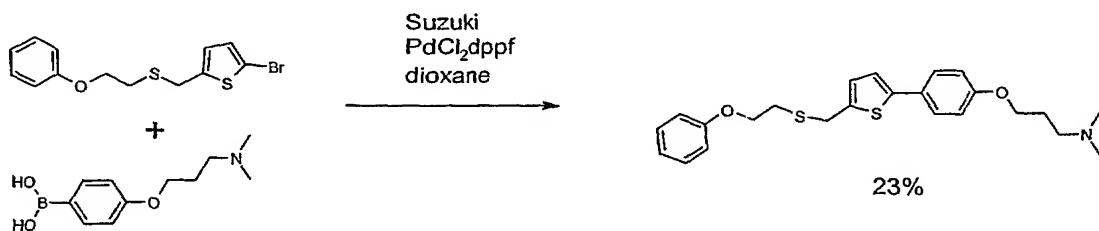
min and stirring at -78 °C continued for 2 h. Temperature was increased to -10 °C over 3 h and then to 0 °C. The mixture was quenched with 1 ml of water and stirred for 80 h at room temperature. The precipitate thus formed was solubilized with 2 ml of methanol and the solution was evaporated after adding 2.5 g silica gel. The coated silica gel was loaded 5 on an aluminum oxide column and eluted with a DCM/DCM-methanol gradient 100 to 90:10 yielding 200 mg (27 %) of the desired compound.

¹H NMR (MeOD) δ 7.62 (d, 2H, br), 6.90 (d, 2H, J=8 Hz), 4.06 (t, 2H, J=4 Hz), 2.63(t, 2H, J=4 Hz), 2.38 (s 6H), and 1.98 (quint., 2H, J=4 Hz). MS (FD) m/e 224.1.

10

Example 190

Dimethyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-thiophen-2-yl]-phenoxy}-propyl)-amine



To a solution of 2-bromo-5-[(2-phenoxy)ethylthio)methyl]-thiophene (247 mg, 0,75 mmol) and [4-[3-(dimethylamino)propoxy]phenyl]boronic acid (200 mg, 0,9mM) in 15 40 ml of argon flushed dioxane was added tetrakis(triphenylphosphine) palladium (0) (87 mg , 0,75 mmol) and 1,5ml 2 M aqueous sodium carbonate (3 mmol) under argon. The mixture was heated to 120 °C for 1h in a microwave oven (MLS ETHOS 1600). TLC showed complete conversion.

20 The reaction mixture was diluted with water and extracted with DCM. The organic phases were dried over sodium sulphate, filtered and evaporated. The residue was purified via flash chromatography on silica gel using a DCM/methanolic ammonia gradient 99:1-95:5 yielding the desired compound almost pure as the free base after two separations.

25 Final purification was achieved via HPLC on RP-18 (acetonitrile/water/0.1% TFA gradient) yielding the trifluoro acetic acid salt as an oil.

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The methanolic solution of the trifluoro acetate was poured on a SCX column, which was rinsed with DCM / methanol and 7N methanolic ammonia to yield the free base. Yield 23%

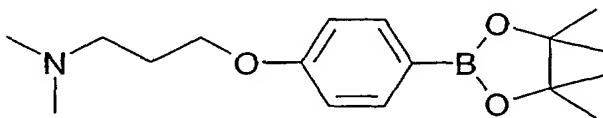
5

Example 191

Alternative Synthesis of dimethyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-thiophen-2-yl]-phenoxy}-propyl)-amine

[4-[3-(dimethylamino)propoxy]phenyl]boronic acid pinacolyl ester (not isolated)

10



15

To a solution of 4-[3-(dimethylamino)propoxy]-iodo benzene(610 mg, 2.00 mmol) in degassed 10 ml DMSO was added bis-(pinacolato)-diborane (558 mg, 2.20 mmol), potassium acetate (200 mg, 6.0 mmol) and 1,1-bis-(diphenylphosphino)-ferrocene-palladium(II)chloride DCM complex (200 mg, 0.24 mmol) under argon. The mixture was stirred by 90 °C for 3 h. MS indicated complete conversion according to boron isotope distribution. To this mixture was added a solution of 2-bromo-5-[{(2-phenoxy)ethylthio)methyl]-thiophene (790 mg , 2.4mM) in 5ml degassed DMSO, PdCl₂dppf DCM complex (192 mg, 0.24 mmol) and 2 M aqueous sodium carbonate (2880 µl , 5.76 mmol) under argon. The mixture was heated to 120°C for 1h in a microwave oven (MLS ETHOS 1600). After 1hour mass spectrometry (MS) showed incomplete conversion. Addition of 0,24 mmol of Pd catalyst and prolonged heating for 1h to 120°C in the microwave oven gave no major improvements. The reaction mixture was extracted with water, DCM and hexane. The organic layers were dried over sodium sulphate, filtered and evaporated. The residue was dissolved in methanol and poured on a 25 5g SCX column, eluted with DCM / methanol and 7N methanolic ammonia and evaporated. The residue was purified via flash chromatography on silica gel using a DCM/methanolic ammonia gradient 99:1-97:3 yielding 250mg (29%) of the desired compound as free base.

The residue was dissolved in methanol/DCM and poured on a column with 2g 30 Amberlite 748 (cation exchange resin) to remove Pd traces.

-364-

The filtrate was evaporated and purified via flash chromatography and prep HPLC on RP-18 (acetonitrile/water/0.1% TFA gradient) yielding 220 mg (20%) of the desired compound as the trifluoroacetic acid salt as a colorless solid.

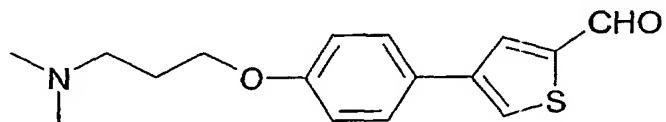
5 Trifluoracetate

¹H NMR (CDCl₃, 300 MHz) δ 11.66 – 11.32 (bs, 1H), 7.52 – 7.43 (d, 2H, *J* = 9Hz), 7.31 – 7.42 (m, 2H), 7.02 – 6.99 (d, 1H, *J* = 4Hz), 6.99 – 6.92 (t, 1H, *J* = 7Hz), 6.92 – 6.82 (m, 5H), 4.18 – 4.06 (t, 2H, *J* = 7Hz), 4.12 – 4.06 (t, 2H, 5Hz), 4.05 – 4.01 (s, 2H), 3.38 – 3.28 (m, 2H), 2.96 – 2.88 (m, 8H) and 2.33 – 2.22 (m, 2H). IR (CHCl₃, cm⁻¹) 1243, 1176, 1059 and 832. MS (ES) m/e 428,1.

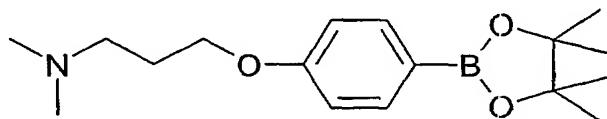
Base

¹H NMR (CDCl₃, 300 MHz) δ 7.47 (d, 2H, *J* = 9 Hz), 7.32 – 7.25 (m, 2H), 7.01 – 6.84 (m, 7H), 4.19 – 4.10 (t, 2H, *J* = 7 Hz), 4.07 – 3.99 (m, 4H), 2.96 – 2.87 (t, 2H, *J* = 7 Hz), 2.5 – 2.40 (t, 2H, *J* = 7Hz), 2.29 – 2.21(s, 6H) and 2.02 – 1.91 (m, 2H). IR (CHCl₃, cm⁻¹) 1246, 1176, 1032 and 832. MS (ES) m/e 428,1. Anal. Calcd for C₂₄H₂₉NO₂S₂: C, 67.41; H, 6.84; N, 3.28; S 15.00. Found C, 66.42; H, 6.59; N, 3.34; S 14.30.

3-[4-(3-dimethylaminopropoxy)-phenyl]-thiophene-5-carboxaldehyde



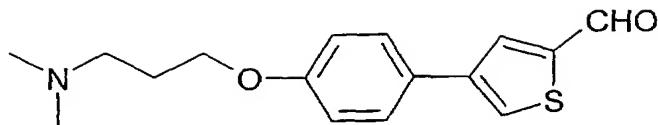
20 [4-[3-(dimethylamino)propoxy]phenyl]boronic acid pinacolyl ester (not isolated)



To a solution of 4-[3-(dimethylamino)propoxy]-iodo benzene(1000 mg, 3.28 mmol) in 20 ml DMSO was added bis-(pinacolato)-diborane (922 mg, 3.63 mmol), potassium acetate (980 mg, 10.0 mmol) and 1.1-bis-(diphenylphosphino)-ferrocene-palladium(II)chloride (82 mg, 0.10 mmol). The mixture was stirred by 80 °C for 3 h. MS indicated complete conversion according to boron isotope distribution. This mixture containing the desired compound was directly used in the next step.

c)

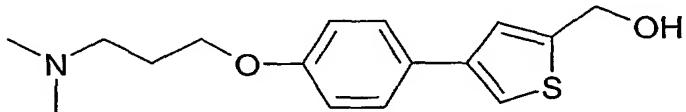
-365-



To a solution of 4-bromo thiophene-2-carboxaldehyde (755 mg, 3.96 mmol) and 1.1-bis-(diphenylphosphino)-ferrocene-palladium(II)chloride dichloromethane complex (82 mg, 0.10 mmol) in 6.60 ml 2M aqueous sodium carbonate (1.32 mmol) was added the 5 DMSO solution of the boronic acid derivative described above and the mixture was stirred for 16 h at 80 °C under argon. The mixture was cooled to room temperature and diluted with DCM. The solution was washed with water and brine, dried and evaporated. The residue was purified via flash chromatography on silica gel using a DCM-ethanolic triethyl amine gradient 99:1 to 90:10 yielding 430 mg of the desired compound (45%).

10 ^1H NMR (CDCl_3) δ 9.98 (s, 1H), 7.99 (d, 1H, $J=1.5$ Hz), 7.75 (d, 1H, $J=1.5$ Hz), 7.50 (d, 2H, $J=8$ Hz), 6.86 (d, 2H $J=8$ Hz), 4.05 (t, 2H, $J=4$ Hz), 2.50 (t 2H, $J=4$ Hz), 2.31 (s, 6H), and 2.00 (quint., 2H, $J=4$ Hz). MS (FD) m/e 290.1.

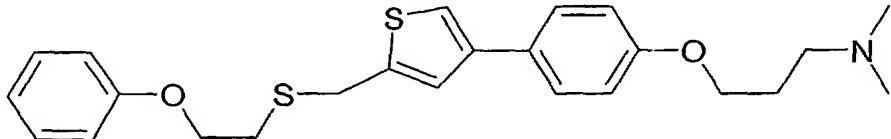
4-[4-(3-dimethylaminopropoxy)phenyl]-thiophene-2-methanol



15 To a solution of 20 % DIBAH in toluene (2.97 ml, 3.6 mmol) was added dropwise a solution of 4-[4-(3-dimethylaminopropoxy)-phenyl]-thiophene-2-carboxaldehyde (430 mg, 1.49 mmol) in 25 ml toluene at 0 to 2 °C. The mixture was stirred for 2 h at 0 to 2 °C and quenched with 5 ml methanol and evaporated. The solid residue was extracted with 20 DCM and ethanol and the collected organic phases dried over sodium sulfate and evaporated. The residue was purified via flash chromatography on silica gel using a DCM-ethanolic ammonia gradient 99:1 to 90:10 yielding 280 mg (65 %) of the desired product.

1 ^1H NMR (CDCl_3) δ 7.48 (d, 2H, $J=8$ Hz), 7.25 (m 2H), 6.96 (d, 2H $J=8$ Hz), 4.80 (s, 2H), 4.03 (t, 2H, $J=4$ Hz), 2.45 (t 2H, $J=4$ Hz), 2.28 (s, 6H), 1.95 (quint., 2H, $J=4$ Hz), and 1.70 (s, br., exch. 1H). MS (FD) m/e 292.1.

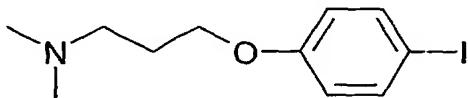
Dimethyl-(3-{4-[4-(2-phenoxy-ethylsulfanylmethyl)-thiophen-2-yl]-phenoxy}-propyl)-amine



To a stirred suspension of 4-[4-(3-dimethylaminopropoxy)phenyl]-2-thiophene-5-methanol (255 mg, 0.87 mmol) in 10 ml of dry THF was added triethyl amine (223 mg, 2.20 mmol) and 10 mg DMAP and the mixture was cooled to -8 to -10 °C. A solution of methane sulfonyl chloride (120 mg, 1.04 mmol) in 2 ml dry THF was added dropwise and the mixture was stirred for 90 min at -5 to 0 °C. TLC showed almost complete conversion. The mixture was quenched with 60 % sodium hydride (42 mg, 1.04 mmol) and stirred for 15 min at 0 °C. In the meantime a solution of sodium 2-phenoxyethanethiolate was prepared from 2-phenoxy ethanethiol (269 mg, 1.74 mmol) and sodium hydride (60%, 71 mg, 1.74 mmol) in 1.5 ml dry THF. After 15 min of stirring the solution was cooled to 0 °C and slowly added to the solution of the mesylate. The mixture was stirred at 0° C for 30 min and then for 16 h at ambient temperature. The mixture was evaporated and the residue purified by repeated chromatography on a silica gel column (DCM/ethanolic ammonia 99:1) yielding 180 mg of the desired product (48%).

¹H NMR (CDCl₃) δ 7.45 (d, 2H, J = 8 Hz), 7.27 (m, 2H), 7.20 (m, 2H), 6.91 (m, 5H,), 4.17 (t, 2H,J=4Hz), 4.05 (t, 2H,J=4Hz + s 2H), 2.95 (t, 2H, J=4Hz), 2.52(t, 2H, J=4Hz), 2.28 (s, 6H), 1.98 (quint., 2H, J=4Hz). MS (FD) m/e 428.2

a) 4-[3-(dimethylamino)propoxy]-iodo benzene

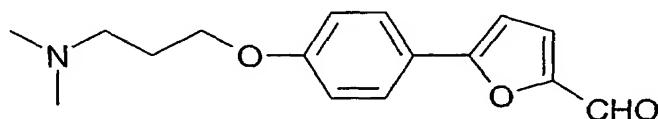


To a suspension of 4-iodo phenol (24.0 g, 110 mmol), anhydrous potassium carbonate (36.0 g, 260 mmol), and potassium iodide (2.2 g, 13 mmol) in 240 ml of dry 2-butanone was added finely ground 3-dimethylamino-1-propyl chloride hydrochloride (13.4 g, 110 mmol). The mixture was stirred under reflux for 48 h. The solvent was distilled off. The residue was dissolved in DCM and extracted with 2N aqueous NaOH

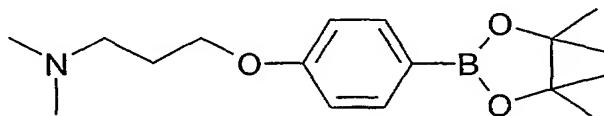
twice. The organic phase was separated washed with water twice, dried and evaporated. The crude oil (21.0 g) was purified via flash chromatography on silica gel using a DCM/ethanolic ammonia gradient (100 to 95:5) yielding 12.9 g of the desired compound sufficiently pure for the next step.

5 ¹H NMR (CDCl₃) δ 7.55 (d, 2H, J=8 Hz), 6.70 (d, 2H, J=8 Hz), 4.00 (t, 2H, J=4 Hz), 2.45(t, 2H, J=4 Hz), 2.23 (s 6H), and 1.95 (quint., 2H, J=4 Hz). MS (FD) m/e 306.0.

b) 2-[4-(3-dimethylaminopropoxy)-phenyl]-furan-5-carboxaldehyde

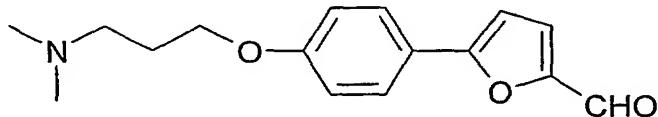


10 b1) [4-[3-(dimethylamino)propoxy]phenyl]boronic acid pinacolyl ester (not isolated)



To a solution of 4-[3-(dimethylamino)propoxy]-iodo benzene(1000 mg, 3.28 mmol) in 20 ml DMSO was added bis-(pinacolato)-diborane (922 mg, 3.63 mmol), potassium acetate (980 mg, 10.0 mmol) and 1.1-bis-(diphenylphosphino)-ferrocene-palladium(II)chloride (82 mg, 0.10 mmol). The mixture was stirred by 80 °C for 3 h. MS indicated complete conversion according to boron isotope distribution. This mixture containing the desired compound was directly used in the next step.

20 c)

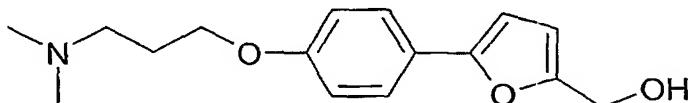


To a solution of 5- bromo furan-2-carboxaldehyde (690 mg, 3.935 mmol) and 1.1-bis-(diphenylphosphino)-ferrocene-palladium(II)chloride dichloromethane complex (82 mg, 0.10 mmol)in 6.60 ml 2M aqueous sodium carbonate (1.32 mmol) was added the DMSO solution of the boronic acid derivative described above and the mixture was stirred for 16 h at 80 °C under argon. The mixture was cooled to room temperature and

diluted with DCM. The solution was washed with water and brine, dried and evaporated. The residue was purified via flash chromatography on silica gel using a DCM-ethanolic triethyl amine gradient 99:1 to 90:10 yielding 500 mg of the desired compound (56%).

¹H NMR (CDCl₃) δ 9.60 (s, 1H), 7.75 (d, 2H, J=6.5 Hz), 7.28 (d, 1H, J=4 Hz), 6.97 (d, 2H J=6.5 Hz), 6.71 (d, 2H, J=4 Hz) 4.07 (t, 2H, J=4 Hz), 2.50 (t 2H, J= 4 Hz), 2.30 (s, 6H,), and 2.00 (quint., 2H, J=4 Hz). MS (FD) m/e 274.1.

5-[4-(3-dimethylaminopropoxy)phenyl]-furan-2-methanol



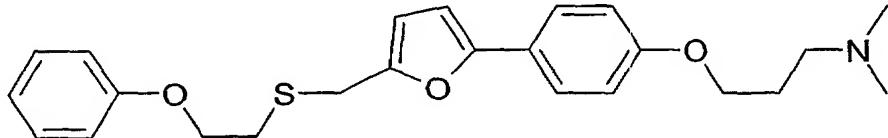
To a solution of 20 % DIBAH in toluene (3.6 ml, 4.4 mmol) was added dropwise a solution of 5-[4-(3-dimethylaminopropoxy)-phenyl]-furan-2-carboxaldehyde (500 mg, 1.83 mmol) in 25 ml toluene at 0 to 2 °C. The mixture was stirred for 2 h at 0 to 2 °C and quenched with 5 ml methanol and evaporated. The solid residue was extracted with DCM and ethanol and the collected organic phases dried over sodium sulfate and evaporated. The residue was purified via flash chromatography on silica gel using a DCM-ethanolic ammonia gradient 99:1 to 95:5 yielding 460 mg (91 %) of the desired product.

¹H NMR (CDCl₃) δ 7.60 (d, 2H, J=7 Hz), 6.90 (d, 2H J=7 Hz) 6.45 (d, 1H, J=3.5 Hz), 6.33 (d, 1H, J=3.5 Hz), 4.66 (s, 2H), 4.00 (t, 2H, J=4 Hz), 2.43 (t 2H, J= 4 Hz), 2.21 (s, 6H), 1.92 (quint., 2H, J=4 Hz), and 1.80 (s, br, exch 1H). MS (FD) m/e 276.2.

20

Example 192

Dimethyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-furan-2-yl]-phenoxy}-propyl)-amine



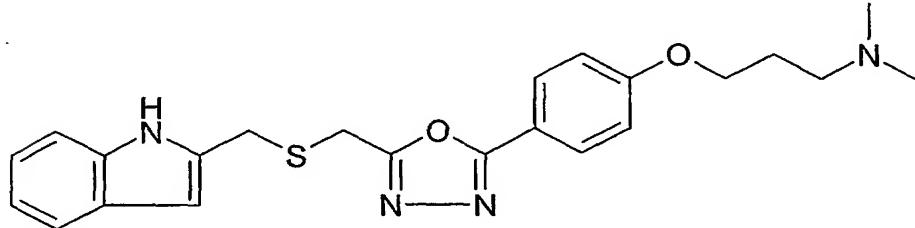
To a stirred solution of 5-[4-(3-dimethylaminopropoxy)phenyl]-2-furan-5-methanol (280 mg, 1.0 mmol) in 16 ml of dry THF was added triethyl amine (258 mg, 2.55 mmol) and 10 mg DMAP and the mixture was cooled to -8 to -10 °C. A solution of methane sulfonyl chloride (138 mg, 1.20 mmol) in 3 ml dry THF was added dropwise and the mixture was stirred for 90 min at -5 to 0 °C. TLC showed almost complete conversion. The mixture was quenched with 60 % sodium hydride (49 mg, 1.20 mmol)

and stirred for 15 min at 0 °C. In the meantime a solution of sodium 2-phenoxyethanethiolate was prepared from 2-phenoxy ethanethiol (309 mg, 2.0 mmol) and sodium hydride (60%, 82 mg, 2.0 mmol) in 2 ml dry THF. After 15 min of stirring the solution was cooled to 0 °C and slowly added to the solution of the mesylate. The mixture was stirred at 0° C for 30 min and then for 16 h at ambient temperature. The mixture was evaporated and the residue purified on a silica gel column. The crude product was further purified by prep. HPLC (RP-18 acetonitrile/water/0.1% TFA) yielding 230 mg of the desired product as the triflate salt (56 %).

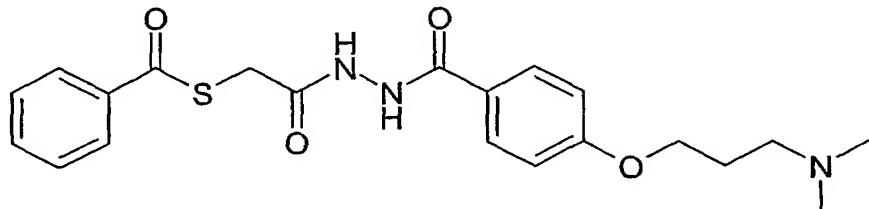
10 ^1H NMR (CDCl_3) δ 7.55 (d, 2H, $J = 8$ Hz), 7.26 (m, 2H), 6.86 (m, 5H), 6.42 (d, 1H, $J=2$ Hz), 6.28 (d, 1H, $J=2$ Hz), 4.14 (t, 2H, $J=4$ Hz), 4.04 (t, 2H, $J=4$ Hz), 3.88 (s, 2H), 2.96 (t, 2H, $J=4$ Hz), 2.45(t, 2H, $J=4$ Hz), 2.30 (s, 6H), 1.95 (quint., 2H, $J=4$ Hz). MS (FD) m/e 412.2.

Example 193

15 Preparation of (3-{4-[5-(1*H*-indol-2-ylmethylsulfanyl)methyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)dimethylamine



20 a) Thiobenzoic acid *S*-(2-{*N'*-[4-(3-dimethylamino-propoxy)benzoyl]hydrazino}-2-oxo-ethyl) ester



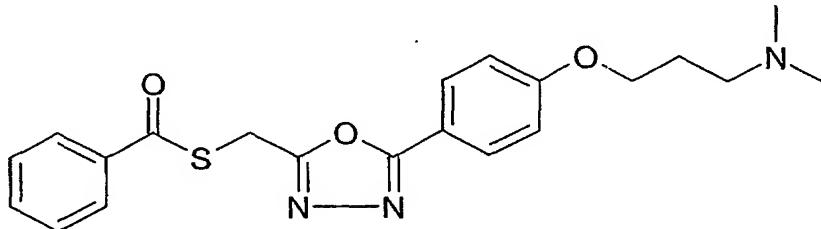
To a solution of benzoylsulfanyl-acetic acid (1.32 g, 6.7 mmol) in 45 ml THF at room temperature was added 1,1'-carbonyldiimidazole. The solution was heated at 60C for eighty minutes then stirred at room temperature for forty minutes. Next, a solution of

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4-[(3-dimethylamino)propoxy]-benzoic acid hydrazide (1.59 g, 6.7 mmol) in 15ml CH₃CN was added to the reaction. The solution was then stirred at room temperature for approximately 22 hours. The resultant suspension was filtered and the insoluble material was rinsed with CH₃CN to afford 1.13 g (40%) of the title compound. The filtrate was 5 concentrated to an oil then treated with water and extracted twice with EtOAc. The combined organic phases were dried over Na₂SO₄, filtered and concentrated to a solid to afford an additional 2.08 g (74%) of the title compound and two impurities. The second lot containing the impurities was used in subsequent reactions.

¹H NMR (DMSO-d6) δ10.28 (bs, 2H), 7.95 (d, 2H, J=7Hz), 7.83 (d, 2H, J=9Hz), 10 7.73 (m ,1H), 7.59 (t, 2H, J=9Hz), 7.00 (d, 2H, J=9Hz), 4.06 (t, 2H, J=6Hz), 3.95 (s, 2H), 2.35 (t, 2H, J=7Hz), 2.14 (s, 6H), 1.83-1.90 (m, 2H). IR (KBr, cm⁻¹) 3280, 2943, 2816, 2769, 1679, 1662, 1654, 1607, 1522, 1497, 1295, 1253, 1211, 919 688. MS (ES⁺) m/e 416. MS (ES⁻) m/e 414.

15 b) Thiobenzoic acid S-{5-[4-(3-dimethylaminopropoxy)phenyl]-[1,3,4]oxadiazol-2-yl} ester

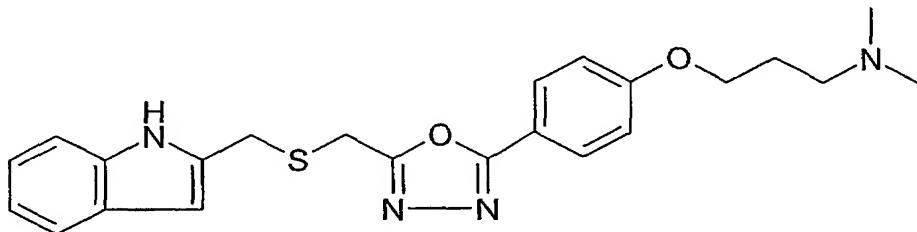


To a solution of Thiobenzoic acid S-(2-{N'-[4-(3-dimethylamino-propoxy)benzoyl]-hydrazino}-2-oxo-ethyl) ester (3.00 g, 7.2 mmol), triphenyl phosphine (3.79 g, 20 14.4 mmol) and triethylamine (1.46 g, 14.4 mmol) at room temperature was added carbon tetrachloride (2.22 g, 14.4 mmol). After stirring one hour at room temperature, carbon tetrabromide (2.39 g, 7.2 mmol) was added. Additional carbon tetrabromide (0.598 g, 1.8 mmol) was added fifteen minutes later. After stirring for approximately 3.5 hours, the resultant suspension was filtered. The filtrate was concentrated to a semi-solid material. 25 Purification by normal phase chromatography (eluted with 9:1 CH₃Cl:MeOH) afforded 2.65 g (92%) of thiobenzoic acid S-{5-[4-(3-dimethylaminopropoxy)phenyl]-[1,3,4]oxadiazol-2-yl} ester s an oil that slowly solidifies.

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¹H NMR (DMSO-d₆) δ7.97 (m, 2H), 7.88 (m, 2H), 7.73 (m, 1H), 7.59 (t, 2H, J=8Hz) 7.12 (m, 2H), 4.69 (s, 2H), 4.08 (t, 2H, J=6Hz), 2.37 (t, 2H, J=7Hz), 2.16 (s, 6H), 1.87 (m, 2H). MS (ES⁺) m/e 398.

- 5 c) (3-{4-[5-(1H-indol-2-ylmethylsulfanyl methyl)-[1,3,4]oxadiazol-2-yl]phenoxy}-propyl)dimethylamine

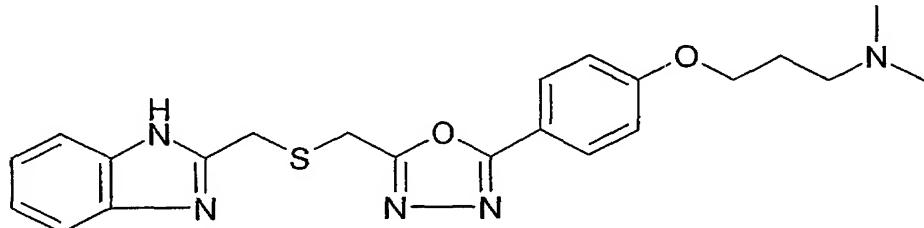


A degassed solution of thiobenzoic acid *S*-{5-[4-(3-dimethylamino propoxy)-phenyl]-[1,3,4]oxadiazol-2-yl} ester (0.264 g, 0.7 mmol) in 1.65 ml MeOH and 0.85 ml H₂O was treated with lithium hydroxide (0.032 g, 1.3 mmol). The reaction was stirred at room temperature for thirty minutes then a mixture of 2-bromomethylindole-1-carboxylic acid methyl ester (0.178 g, 0.7 mmol) in 1 ml MeOH and 2 ml THF was added. After stirring at room temperature for three hours the mixture was concentrated to remove bulk of methanol. The mixture was diluted with EtOAc then washed twice with water and once with brine. The organic layer was dried over Na₂SO₄, filtered and was concentrated to an oil. Purification by normal phase radial chromatography (eluted with 5% 2M NH₃ in MeOH:CHCl₃) afforded a solid. Crystallization of the solid from Et₂O:MeOH afforded 0.066 g (17%) of (3-{4-[5-(1H-indol-2-ylmethylsulfanyl methyl)-[1,3,4]oxadiazol-2-yl]phenoxy}-propyl)dimethylamine.

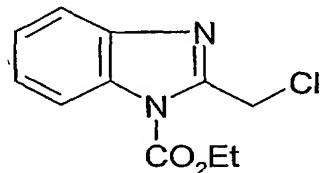
20 ¹H NMR (DMSO-d₆) δ11.11 (bs, 1H), 7.84 (d, 2H, J=9Hz), 7.44 (d, 1H, J=8Hz), 7.31 (d, 1H, J=8Hz), 7.11 (d, 2H, J=9Hz), 7.04 (t, 1H, J=7Hz), 6.95 (t, 1H, J=7Hz), 6.38 (s, 1h), 4.09 (t, 2H, J=6Hz), 4.02 (s, 4H), 2.36 (t, 2H, J=7Hz), 2.15 (s, 6H), 1.87 (m, 2H). IR (KBr, cm⁻¹) 3425, 3050, 2942, 2757, 1617, 1499, 1256, 1175, 732. MS (ES⁺) m/e 423. MS (ES⁻) m/e 421. Anal. Calcd for C₂₃H₂₆N₄O₂S C, 65.38; H, 6.20; N, 13.26. Found C, 25 65.00; H, 6.17; N, 13.12.

Example 194

Preparation of (3-{4-[5-(1H-Benzimidazol-2-ylmethylsulfanyl)methyl]-[1,3,4]-oxadiazol- 2-yl]phenoxy}propyl)dimethyl amine



- 5 a) 2-Chloromethylbenzoimidazole-1-carboxylic acid *tert*-butyl ester

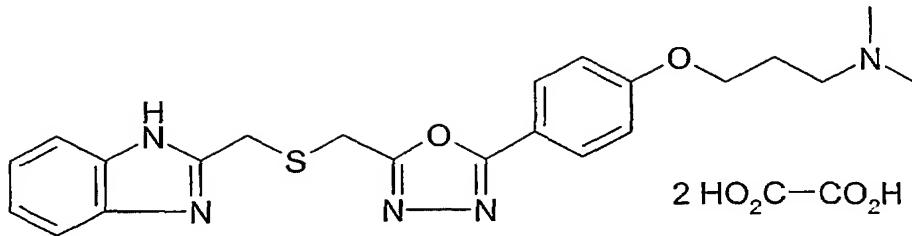


A mixture of 2-(chloromethyl)benzimidazole (4.05 g, 24.3 mmol), 4-dimethylamino pyridine (0.297 g, 2.4 mmol) and di-*tert*-butyl dicarbonate (6.37 g, 29.2 mmol) in 48 ml CH₃CN was stirred at room temperature for four hours. Next, the 10 suspension was heated at 60C for 30 minutes. Upon cooling to room temperature the mixture was concentrated to an oil. The mixture was treated with 100 ml each of 1N HCl and Et₂O and the resultant suspension was filtered. The phases from the filtrate were separated and the organic phase was washed with 1N HCl (2 x 100 ml), brine then concentrated to an oil. Purification by normal phase chromatography (eluted with 70% hexane:EtOAc) afforded 2.23 g (34%) of 2-chloromethylbenzoimidazole-1-carboxylic acid *tert*-butyl ester as an oil.

15 ¹H NMR (DMSO-d6) δ8.06 (d, 1H, J=10Hz), 7.61 (d, 1H, J=8Hz), 7.21-7.37 (m, 2H), 7.00 (s, 1H), 5.99 (s, 2H), 4.05 (s, 3H). IR (KBr, cm⁻¹) 3455, 2980, 2934, 2869, 1709, 1606, 1509, 1454, 1367, 1244, 1169. Anal. Calcd for C₁₃H₁₅CIN₂O₂ C, 58.54; H, 5.67; N, 10.50. Found C, 58.55; H, 5.93; N, 10.42.

- 20 b) (3-{4-[5-(1H-benzoimidazol-2-ylmethylsulfanyl)methyl]-[1,3,4]-oxadiazol- 2-yl]phenoxy}propyl)dimethyl amine.

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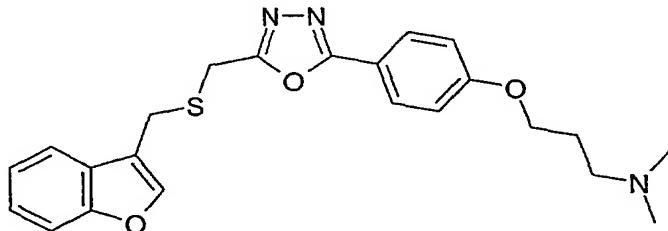
The above compound was prepared in a manner similar to that exemplified for the preparation of 193c, from thiobenzoic acid *S*-{5-[4-(3-dimethylaminopropoxy)phenyl]-[1,3,4]oxadiazol-2-yl} ester (0.264 g, 0.7 mmol), lithium hydroxide (0.032 g, 1.3 mmol) and 2-chloromethylbenzoimidazole-1-carboxylic acid *tert*-butyl ester (0.178 g, 0.7 mmol) in 1ml MeOH to afford 0.118 g of an oil. The oil was dissolved into acetone and treated with 0.038 g of oxalic acid in acetone to afford 0.121 g (36%) of (3-{4-[5-(1H-benzoimidazol-2-ylmethyl-sulfanylmethyl)-[1,3,4]-oxadiazol-2-yl]phenoxy}propyl)dimethyl amine as the dioxalate salt.

¹H NMR (DMSO-d₆) δ11.11 (bs, 1H), 7.84 (d, 2H, J=9Hz), 7.44 (d, 1H, J=8Hz), 7.31 (d, 1H, J=8Hz), 7.11 (d, 2H, J=9Hz), 7.04 (t, 1H, J=7Hz), 6.95 (t, 1H, J=7 Hz), 6.38 (s, 1H), 4.09 (t, 2H, J=6Hz), 4.02 (s, 4H), 2.36 (t, 2H, J=7Hz), 2.15 (s, 6h), 1.87 (m, 2H). IR (KBr, cm⁻¹) 3425, 3050, 2942, 2757, 1617, 1499, 1256, 1175, 732. MS (ES⁺) m/e 424. MS (ES⁻) m/e 422.

Example 195

Preparation of (3-{4-[5-Benzofuran-3-ylmethylsulfanyl]-[1,3,4]-oxadiazol-2-yl]phenoxy}propyl)dimethylamine.

20



The above compound was prepared in a manner similar to that exemplified for the preparation of 193c, from thiobenzoic acid *S*-{5-[4-(3-dimethylaminopropoxy)phenyl]-[1,3,4]oxadiazol-2-yl} ester (0.622 g, 1.6 mmol), lithium hydroxide (0.075 g, 3.1 mmol)

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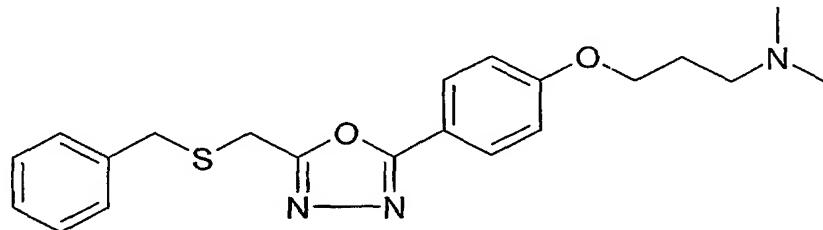
and 3-bromomethylbenzofuran (0.331 g, 1.6 mmol) in 2.3 ml MeOH. Crystallization from Et₂O afforded 0.202 g (30%) of (3-{4-[5-benzofuran-3-ylmethylsulfanyl]-[1,3,4]-oxadiazol-2-yl]phenoxy}propyl) dimethyl- amine.

¹H NMR (DMSO-d6) δ7.95 (s, 1H), 7.83 (d, 2H, J=9Hz), 7.72 (m ,1H), 7.54 (d, 5 1H, J=8Hz), 7.23-7.43 (m, 2H), 7.11 (D, 2h, J=9 Hz), 4.09 (t, 2H, J=7Hz), 4.03 (s, 2H), 4.01 (s, 2H), 2.36 (t, 2H, J=7Hz), 2.14 (s, 6H), 1.83-1.92 (m, 2H). IR (KBr, cm⁻¹) 2817, 2766, 1611, 1502, 1472, 1452, 1302, 1258, 1179, 1101, 1089, 1004, 839, 746. MS (ES⁺) m/e 424. Anal. Calcd for C₂₃H₂₅N₃O₃S C, 65.23; H, 5.95; N, 9.92. Found C, 65.27; H, 6.22; N, 9.65. Mp(°C)=85.

10

Example 196

Preparation of (3-{4-[5-Benzylsulfanylmethyl]-[1,3,4]-oxadiazol-2-yl]phenoxy}propyl)dimethylamine.



15

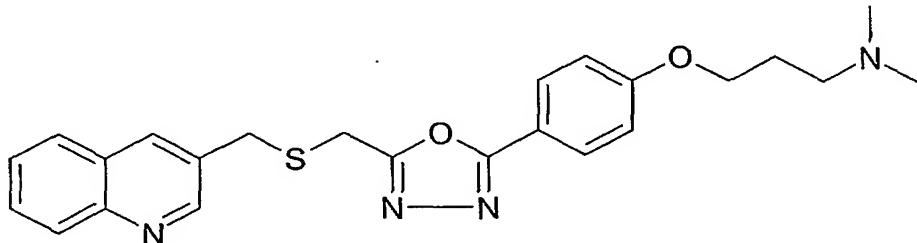
The above compound was prepared in a manner similar to that exemplified for the preparation of 193c, from thiobenzoic acid S-{5-[4-(3-dimethylaminopropoxy)phenyl]-[1,3,4]oxadiazol-2-yl} ester (0.220 g, 0.5 mmol), lithium hydroxide (0.026 g, 1.1 mmol) and benzyl bromide (0.095 g, 0.6 mmol) in 0.9 ml MeOH to afford 0.087 g (41%) of (3-{4-[5-Benzylsulfanylmethyl]-[1,3,4]-oxadiazol-2-yl}phenoxy}propyl)dimethylamine as a crystalline solid.

20

¹H NMR (DMSO-d6) δ7.89 (d, 2H, J=9Hz), 7.21-7.38 (m, 5H), 7.12 (d, 2H, J=9Hz), 4.09 (t, 2H, J=6Hz), 3.95 (s, 2H), 3.86 (s, 2H), 2.36 (t, 2H, J=7Hz), 2.15 (s, 6H), 1.83-1.92 (m, 2H). IR (KBr, cm⁻¹) 2761, 1614, 1565, 1499, 1473, 1246, 1175, 1049, 838, 701. MS (ES⁺) m/e 384. Anal. Calcd for C₂₁H₂₅N₃O₃S C, 65.77; H, 6.57; N, 10.96. Found C, 65.54; H, 6.50; N, 10.83.

Example 197

Preparation of Dimethyl-(3-{4-[5-(quinolin-2-ylmethylsulfanyl)methyl]-[1,3,4]oxadiazol-2-yl}phenoxy)propyl)amine.



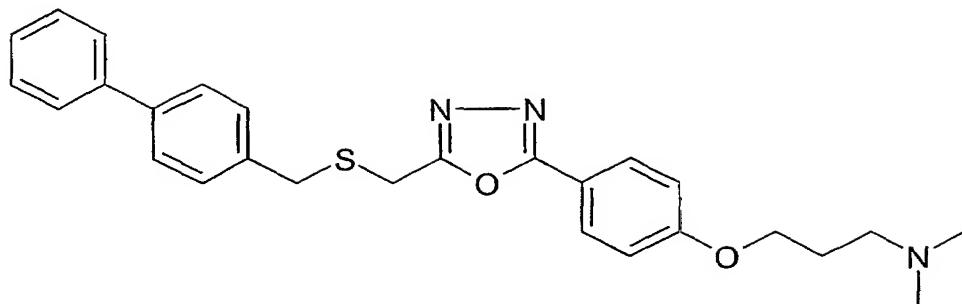
5 The above compound was prepared in a manner similar to that exemplified for the preparation of 193c, from thiobenzoic acid *S*-{5-[4-(3-dimethylaminopropoxy)phenyl]-[1,3,4]oxadiazol-2-yl} ester (0.344 g, 0.9 mmol), lithium hydroxide (0.062 g, 2.6 mmol) and 2-chloromethyl quinoline HCl (0.184 g, 0.9 mmol) in 1.4 ml MeOH to afford 0.182 g of an oil. A solution of ethanol (0.194 g, 4.2mmol) in Et₂O was treated with acetyl
10 chloride (0.131 g, 1.7 mmol) to generate HCl *in situ*. After stirring five minutes this solution was added to a solution of the title compound in Et₂O. The resultant suspension was filtered to afford 0.204 g (50%) of dimethyl-(3-{4-[5-(quinolin-2-ylmethylsulfanyl-methyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)amine monohydrochloride salt.

15 ¹H NMR (DMSO-d₆) δ8.30 (d, 1H, J=8Hz), 7.90-7.94 (m, 2H), 7.78 (d, 2H, J=9Hz), 7.69-7.75 (m, 1H), 7.53-7.60 (m, 2H), 7.09 (d, 2H, J=9Hz), 4.15-4.18 (m, 6H), 3.19-3.24 (m, 2H), 2.78 (s, 6H), 2.13-2.23 (m, 2H). IR (KBr, cm⁻¹) 2954, 2632, 2607, 2483, 1615, 1499, 1486, 1473, 1260, 1242, 1183, 837, 827, 759. MS (ES⁺) m/e 435. Anal. Calcd for C₂₄H₂₆N₄O₂S HCl C, 61.20; H, 5.78; N, 11.89. Found C, 60.86; H, 5.77; N, 11.90. Mp(°C)=190.

20

Example 198

Preparation of (3-{4-[5-(Biphenyl-4-ylmethylsulfanyl)methyl]-[1,3,4]oxadiazol-2-yl}phenoxy)propyl)dimethylamine.

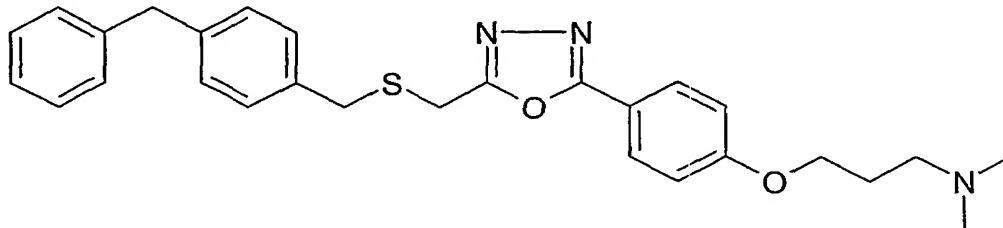


The above compound was prepared in a manner similar to that exemplified for the preparation of 193c, from thiobenzoic acid *S*-{5-[4-(3-dimethylaminopropoxy)phenyl]-[1,3,4]oxadiazol-2-yl} ester (0.207 g, 0.5 mmol), lithium hydroxide (0.025g, 1.0 mmol) and 4-bromomethylbiphenyl (0.129 g, 0.5 mmol). After stirring at room temperature for three hours the suspension was filtered. The insoluble material was dissolved into EtOAc:MeOH and purified by normal phase silica gel chromatography (eluted with 5% 2M NH₃ in MeOH:CH₂Cl₂) to afford a white solid. This material was then converted to the HCl as described in Example 5 using the acetyl chloride/EtOH method to generate HCl *in situ* to afford 0.112 g (43%) of (3-{4-[5-(Biphenyl-4-ylmethylsulfanyl)methyl]-[1,3,4]oxadiazol-2-yl]phenoxy}propyl) dimethyl- amine as the hydrochloride salt.

¹H NMR (DMSO-d6) δ7.88 (d, 2H, J=9Hz), 7.59 (d, 4H, J=8Hz), 7.33-7.47 (m, 5H), 7.11 (d, 2H, J=9Hz), 4.14 (t, 2H, J=6Hz), 4.00 (s, 2H), 3.91 (s, 2H), 3.19-3.24 (m, 2H), 2.78 (s, 6H), 2.13-2.22 (m, 2H). IR (KBr, cm⁻¹) 3491, 2956, 2599, 2470, 1617, 1587, 1566, 1501, 1484, 1428, 1393, 1308, 1258, 1171, 1087, 1054, 1003, 834, 695. MS (ES⁺) m/e 460. Analytical HPLC: 100%. Mp(°C)=191.

Example 199

Preparation of (3-{4-[5-(4-Benzyl-benzylsulfanyl)methyl]-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)dimethylamine



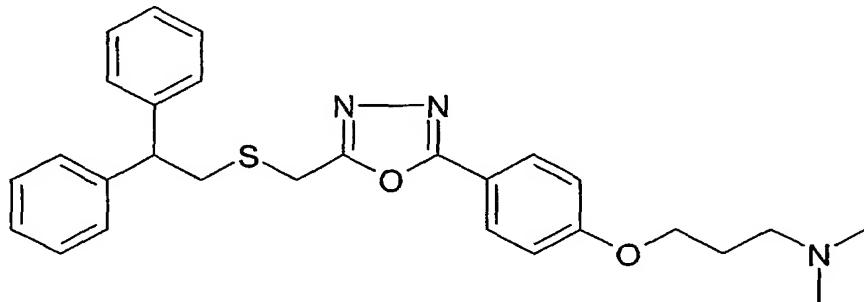
The above compound was prepared in a manner similar to that exemplified for the preparation of 193c, from thiobenzoic acid *S*-{5-[4-(3-dimethylaminopropoxy)phenyl]-[1,3,4]oxadiazol-2-yl} ester (0.206 g, 0.5 mmol), lithium hydroxide (0.025 g, 1.0 mmol) and 4-benzyl-benzylmethyl bromide (0.135 g, 0.5 mmol) in 1 ml MeOH. Purification by 5 normal phase silica gel chromatography (eluted with 5% 2M NH₃ in MeOH:CH₂Cl₂ to 10% 2M NH₃ in MeOH:CH₂Cl₂) afforded an oil. This material was then converted to the HCl as described in Example 5 using the acetyl chloride/EtOH method to generate HCl *in situ* to afford 0.073 g (28%) of (3-{4-[5-(4-Benzyl-benzylsulfanyl)methyl]-[1,3,4]oxadiazol-2-yl]phenoxy}propyl di-methylamine as the hydrochloride salt.

10 ¹H NMR (DMSO-d6) δ7.90 (d, 2H, J=9Hz), 7.11-7.32 (m, 11H), 4.16 (t, 2H, J=6Hz) 3.94 (s, 2H), 3.88 (s, 2H), 3.82 (s, 2H), 3.22 (t, 2H, J=8Hz), 2.77 (s, 6H), 2.13-2.23 (m, 2H). IR (KBr, cm⁻¹) 3482, 3024, 2933, 2599, 2475, 1616, 1500, 1428, 1307, 1257, 1173, 1053, 1002, 835, 724, 699. MS (ES⁺) m/e 474. Mp(°C)=151.

15

Example 200

Preparation of (3-{4-[5-(2,2-diphenylethylsulfanyl)methyl]-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)dimethylamine



The above compound was prepared in a manner similar to that exemplified for the 20 preparation of 193c, from thiobenzoic acid *S*-{5-[4-(3-dimethylaminopropoxy)phenyl]-[1,3,4]oxadiazol-2-yl} ester (0.233 g, 0.6 mmol), lithium hydroxide (0.028 g, 1.2 mmol) and 2,2-diphenylethylbromide (0.153 g, 0.6 mmol). The reaction was stirred at room 25 temperature for 3 hours then heated at 60C for 2 two days. Purification by normal phase silica gel chromatography (eluted with 5% 2M NH₃ in MeOH:CH₂Cl₂ to 10% 2M NH₃ in MeOH:CH₂Cl₂) afforded an oil. This material was then converted to the HCl as described in Example 5 using the acetyl chloride/EtOH method to generate HCl *in situ* to

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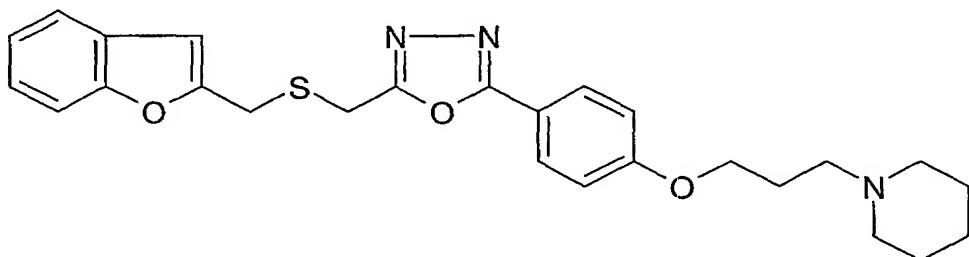
afford 0.104 g (35%) of (3-{4-[5-(2,2-diphenylethylsulfanyl methyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)dimethylamine as the hydrochloride salt.

¹H NMR (DMSO-d₆) δ7.88 (d, 2H, J=9Hz), 7.23-7.31 (m, 8H), 7.12-7.18, m, 4H), 4.22 (t, 1H, J=8Hz), 4.16 (t, 2H, J=6Hz), 4.09 (s, 2H), 3.35 (d, 2H, J=8Hz), 3.21 (t, 2H, J=8Hz), 2.77 (s, 6H), 2.08-2.21 (m, 2H). IR (KBr, cm⁻¹) 3436, 3024, 2954, 2594, 2478, 1734, 1613, 1568, 1501, 1452, 1302, 1259, 1176, 1051, 839, 734, 706, 530. MS (ES⁺) m/e 474. Mp(°C)=149.

Example 201

Preparation of (3-{4-[5-(Benzofuran-2-ylmethylsulfanyl methyl)-[1,3,4]oxadiazol-2-

10 yl]phenoxy}propyl)dimethylamine



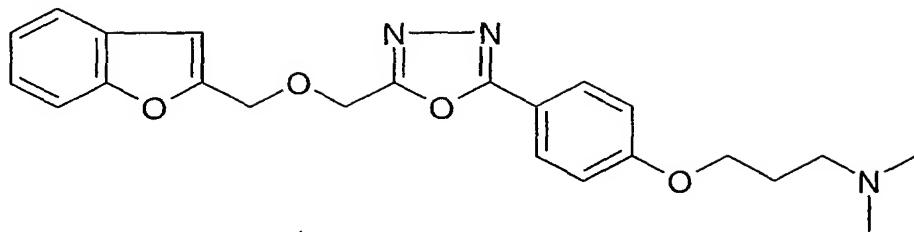
The above compound was prepared in a manner similar to that exemplified for the preparation of 193c, from thiobenzoic acid *S*-{5-[4-(3-dimethylaminopropoxy)phenyl]-[1,3,4]oxadiazol-2-yl} ester (0.633 g, 1.4 mmol), lithium hydroxide (0.069 g, 2.9 mmol) and benzofuran-2-ylmethyl bromide (0.305 g, 1.4 g). Crystallization of the isolated product from Et₂O afforded 0.246 g (37%) of (3-{4-[5-(Benzofuran-2-ylmethylsulfanyl methyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)dimethylamine.

¹H NMR (DMSO-d₆) δ7.79 (d, 2H, J=9Hz), 7.52 (d, 1H, J=7Hz), 7.44 (d, 1H, J=8Hz), 7.16-7.24 (m, 2H), 7.07 (d, 2H, J=9Hz), 6.78 (s, 1H), 4.07-4.13 (m, 6H), 2.27-2.40 (m, 6H), 1.85-1.91 (m, 2H), 1.45-1.52 (m, 4H), 1.34-1.40 (m, 2H). IR (KBr, cm⁻¹) 2933, 2769, 1611, 1501, 1452, 1393, 1300, 1249, 1174, 1130, 1089, 1049, 1005, 950, 839, 815, 761. MS (ES⁺) m/e 464. Anal. Calcd for C₂₆H₂₉N₃O₃S C, 67.36; H, 6.31; N, 9.00. Found C, 67.50; H, 6.52; N, 9.03. Mp(°C)=114.

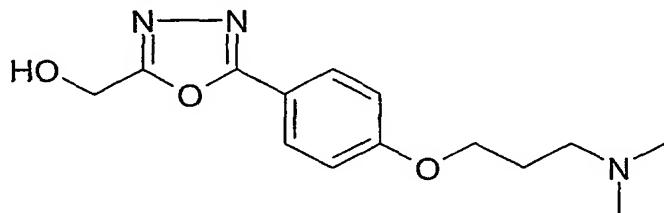
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Example 202

Preparation of (3-{4-[5-(Benzofuran-2-ylmethoxymethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)dimethylamine



a) {5-[4-(3-Dimethylaminopropoxy)phenyl]-[1,3,4]oxadiazol-2-yl} methanol

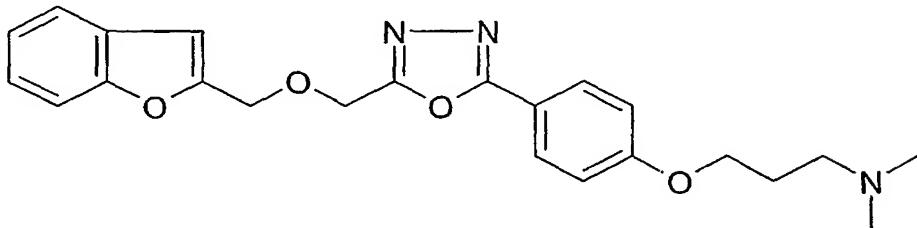


To a solution of acetoxy acetic acid (0.249 g, 2.1 mmol) in 9 ml THF at room temperature was added 1,1'-carbonyldiimidazole (0.342 g, 2.1 mmol). The solution was heated at 60C for 80 minutes, then stirred at room temperature for 40 minutes. The solution was then treated with 4-[(3-dimethylamino)propoxy]-benzoic acid hydrazide (0.500 g, 2.1 mmol). The resultant light suspension was stirred at room temperature for 1.5 hours. Next, the suspension was treated with triphenyl phosphine (1.11 g, 4.2 mmol) and carbon tetrabromide (1.40 g, 4.2 mmol). The reaction was stirred an additional three hours before being concentrated to a semi-solid material. The crude material was treated with 5.4 ml MeOH and 1.6 ml H₂O then lithium hydroxide (0.151 g, 6.3 mol) was added. After stirring at room temperature for 1.45 hours the reaction was concentrated in volume then extracted three times with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄, filtered, then concentrated to an oil. Purification by normal phase silica gel radial chromatography (eluted with 9:1 CHCl₃:2M NH₃ in MeOH) afforded 0.339 g (58%) of {5-[4-(3-dimethylaminopropoxy)phenyl]-[1,3,4]oxadiazol-2-yl}methanol.

¹H NMR (DMSO-d6) δ7.92 (d, 2H, J=9Hz), 7.13 (d, 2H, J=9Hz), 5.92 (t, 1H, J=6Hz), 4.68 (d, 2H, J=6Hz), 4.09 (t, 2H, J=6Hz), 2.36 (t, 2H, J=7Hz), 2.12 (s, 6H), 1.83-1.92 (m, 2H). IR (KBr, cm⁻¹) 2873, 2788, 1613, 1588, 1500, 1467, 1309, 1258, 1179, 1055, 1003, 742, 675, 534. MS (ES⁺) m/e 278.

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- b) (3-{4-[5-(Benzofuran-2-ylmethoxymethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)- dimethylamine



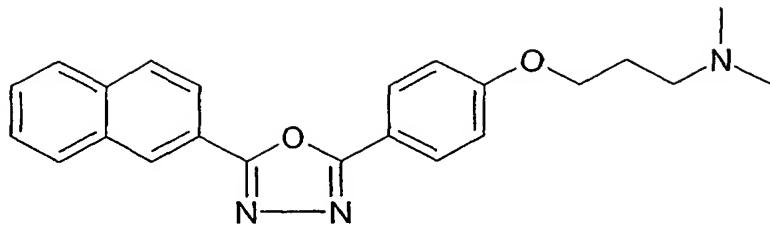
To a solution of {5-[4-(3-dimethylaminopropoxy)phenyl]-[1,3,4]oxadiazol-2-yl}methanol (0.150 g, 0.5mmol) in 2.5 ml DMF at room temperature was added 60% sodium hydride (0.023 g, 0.6mmol). After stirring at room temperature for one hour an additional 2 ml DMF was added followed by 2-(bromomethyl)naphthalene (0.120 g, 0.5 mmol). Approximately one hour later additional 60% sodium hydride (0.023 g, 0.6 mmol) was added. The reaction was treated with H₂O and extracted three times with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄, filtered, and concentrated to an oil. Purification by normal phase silica gel radial chromatography (eluted with 95:5 CHCl₃:2M NH₃ in MeOH) to afford an oil. This material was then converted to the HCl as described in Example 5 using the acetyl chloride/EtOH method to generate HCl *in situ* to afford 0.063 g (26%) of (3-{4-[5-(Benzofuran-2-ylmethoxymethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)dimethyl- amine as the hydrochloride salt.

¹H NMR (DMSO-d6) δ7.88-7.97 (m, 6H), 7.49-7.55 (m, 3H), 7.15 (d, 2H, J=9 Hz), 4.88 (s, 2H), 4.82 (s, 2H), 4.17 (t, 2H, J=6Hz), 3.22 (t, 2H, J=8Hz), 2.76 (s, 6H), 2.13-2.23 (m, 2H). IR (KBr, cm⁻¹) 2472, 1616, 1500, 1472, 1257, 1089. MS (ES⁺) m/e 418. Anal. Calcd for C₂₅H₂₇N₃O₃ HCl C, 66.14; H, 6.22; N, 9.26. Found C, 65.74; H, 6.11; N, 9.14. Mp(°C)=173.

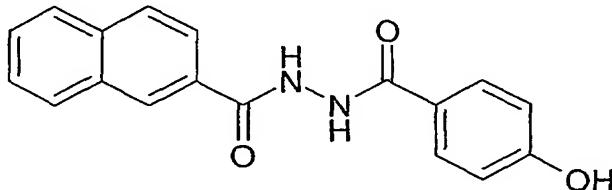
Example 203

Preparation of Dimethyl-{3-[4-(5-naphthalene-2-yl-[1,3,4]oxadiazol-2-yl)phenoxy}-propyl}amine

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a) 4-Hydroxybenzoic acid *N'*-(naphthalene-2-carbonyl)hydrazide



5 To a solution of 2-naphthoic acid (2.01 g, 11.7 mmol) in 30 ml DMF at OC was added fluoro-N,N,N',N'-tetramethylformamidinium hexafluoro phosphate (3.08 g, 11.7 mmol). The reaction was stirred at 0C for fifteen minutes then triethylamine (2.36 g, 23.3 mmol) and a suspension of 4-hydroxybenzoic hydrazide (3.55 g, 23.3 mmol) in 30 ml DMF, were added. The reaction was then stirred at room temperature for thirty minutes.

10 Next, the resultant solution was slowly poured into 600 ml of ice water. The resultant suspension was filtered. The insoluble material was triturated in 500ml 5N HCl until a fine suspension resulted. The insoluble material was collected by filtration then treated with 300 ml boiling MeOH. The milky suspension was filtered and the filtrate was reduced in volume on a steam bath until crystals started forming. The crystalline material

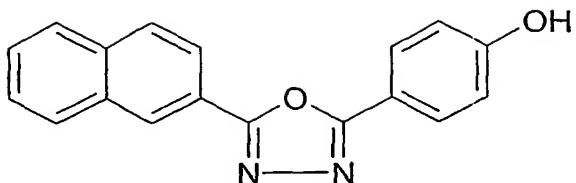
15 was collected by filtration to afford 1.63 g (46%) of 4-Hydroxybenzoic acid *N'*-(naphthalene-2-carbonyl)hydrazide.

¹H NMR (DMSO-d₆) δ10.55 (s, 1H), 10.30 (s, 1H), 10.11 (s, 1H), 8.55 (s, 1H), 7.97-8.08 (m, 4H), 7.82 (d, 2H, J=8Hz), 7.59-7.68 (m, 2H), 6.86 (d, 2H, J=8Hz). IR (KBr, cm⁻¹) 3339, 1734, 1676, 1645, 1583, 1506, 1437, 1377, 1276, 1238, 1170, 779, 757, 547,

20 MS (ES⁻) m/e 305.

a) 4-(5-Naphthalen-2-yl-[1,3,4]oxadiazol-2-yl)phenol

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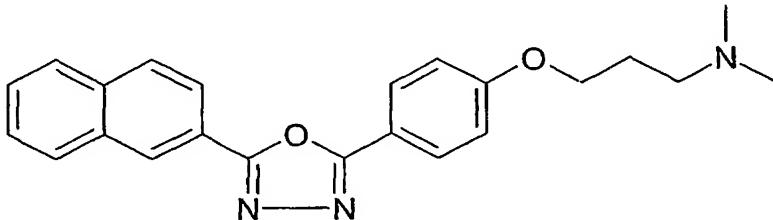


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19d, from 4-Hydroxybenzoic acid *N'*-(naphtha-1-ene-2-carbonyl)hydrazide (1.57 g, 5.1 mmol), triphenylphosphine (2.69 g, 10.3 mmol), triethylamine (1.66 g, 16.4 mmol) and carbon tetrabromide (3.40 g, 10.3 mmol) to afford an oil.

- 5 The oil was treated with 100 ml EtOAc. The resultant precipitate was collected by filtration and discarded. The filtrate was concentrated to an oil. Purification by normal phase silica gel chromatography (eluted with 3:2 hexane:EtOAc) afforded 0.220 g (15%) of 4-(5-Naphthalen-2-yl-[1,3,4]oxadiazol-2-yl)phenol.

10 ^1H NMR (DMSO-d₆) δ 10.36 (s, 1H), 8.74 (s, 1H), 8.13-8.18 (m, 3H), 8.01-8.08 (m, 3H), 7.64-7.70 (m, 2H), 7.01 (d, 2H, J=9Hz). IR (KBr, cm⁻¹) 1735, 1610, 1589, 1504, 1443, 1292, 1171, 844, 751. MS (ES⁺) m/e 289, MS (ES⁻) m/e 287

c) Dimethyl-{3-[4-(5-naphthalene-2-yl-[1,3,4]oxadiazol-2-yl)phenoxy]propyl}amine.



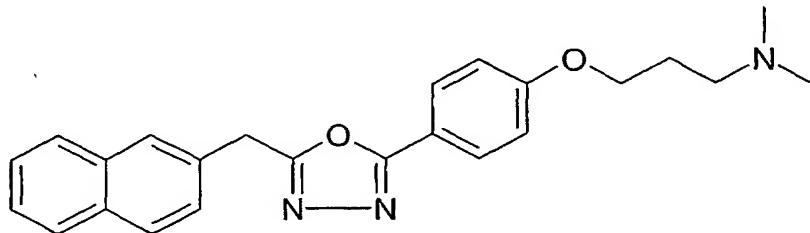
15

The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19e, from 4-(5-naphthalen-2-yl-[1,3,4]oxadiazol-2-yl)phenol (0.205 g, 0.7 mmol), sodium hydride (0.057g, 1.4 mmol) and 3-chloro-N,N-dimethylpropyl amine HCl (0.112g, 0.7 mmol) to afford the title compound as a crude material. Purification by radial chromatography on silica gel (eluted with 9:1 Et₂O: 2M NH₃ in MeOH) afforded 0.120 g (45%) of dimethyl-{3-[4-(5-naphthalene-2-yl-[1,3,4]-oxadiazol-2-yl)phenoxy]propyl}amine as a solid.

20 ^1H NMR (DMSO-d₆) δ 8.76 (s, 1H), 8.01-8.21 (m, 6H), 7.64-7.70 (m, 2H), 7.18 (d, 2H, J=9Hz), 4.13 (t, 2H, J=6Hz), 2.38 (t, 2H, J=7Hz), 2.13 (s, 6H), 1.85-1.94 (m, 2H).
25 IR (KBr, cm⁻¹) 1613, 1498, 1464, 1257, 1175. MS (ES⁺) m/e 374. Mp(°C)=127.

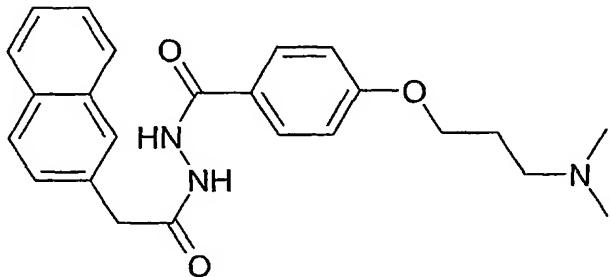
Example 204

Preparation of Dimethyl- {3-[4-(5-naphthalene-2-ylmethyl-[1,3,4]oxadiazol-2-yl)-phenoxy]propyl} amine



5

a) 4-(3-Dimethylaminopropoxy)benzoic acid *N'*-(2-naphthalen-2-ylacetyl)hydrazide

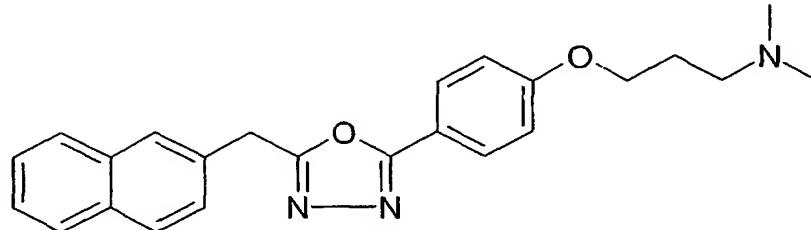


To a solution of 2-naphthyl acetic acid (0.237 g, 1.3 mmol) in 5.6 ml THF at room temperature was added 1,1'-carbonyldiimidazole (0.206 g, 1.3mmol). The solution was heated at 60C for one hour. Upon cooling to room temperature, the reaction was treated with 4-[(3-dimethylamino)propoxy]-benzoic acid hydrazide (0.302 g, 1.3 mmol). The reaction was stirred at room temperature for four hours then concentrated to an oil. The oil was treated with 25 ml 0.1 N NaOH and extracted with EtOAc (2 x 25 ml). A precipitate develop in the aqueous phase. The precipitate was collected by filtration to afford 0.306 g (59%) of 4-(3-Dimethylaminopropoxy)benzoic acid *N'*-(2-naphthalen-2-ylacetyl)hydrazide.

¹H NMR (DMSO-d6) δ10.21 (bs, 2H), 7.81-7.91 (m, 6H), 7.45-7.53 (m, 3H), 6.99(d, 2H, J=9Hz), 4.05 (t, 2H, J=6Hz), 3.71 (s, 2H), 2.34 (t, 2H, J=7Hz), 2.10 (s, 6H), 1.80-1.89(m, 2H). IR (CHCl₃, cm⁻¹) 1682, 1631, 1608, 1510, 1463, 1255, 1174. MS (ES⁺) m/e 406, MS (ES⁻) m/e 404.

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- b) Dimethyl-{3-[4-(5-naphthalene-2-ylmethyl-[1,3,4]oxadiazol-2-yl)- phenoxy] propyl}- amine

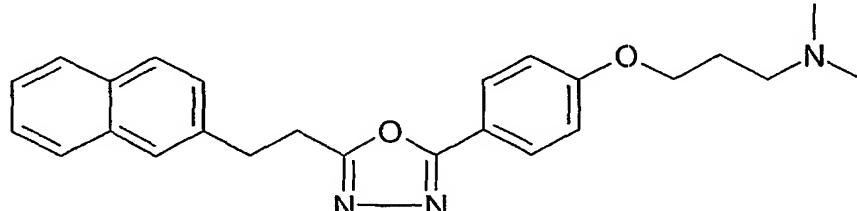


The above compound was prepared in a manner similar to that exemplified for the
 5 preparation of Example 19d, from 4-(3-Dimethylaminopropoxy)benzoic acid *N'*-(2-naphthalen-2-ylacetyl)hydrazide (0.436 g, 1.1 mmol), triphenylphosphine (0.564 g, 2.2 mmol), triethylamine (0.218 g, 2.2 mmol) and carbon tetrabromide (0.713 g, 2.2 mmol) to afford an oil. Purification by normal phase silica gel chromatography (eluted with 9:1 Et₂O:2M NH₃ in MeOH) followed by conversion to the HCl salt as described in Example
 10 5 using the acetyl chloride/EtOH method to generate HCl *in situ* afforded 0.235 g (52%) of dimethyl-{3-[4-(5-naphthalene-2-ylmethyl-[1,3,4]oxadiazol-2-yl)phenoxy] propyl}amine as the hydrochloride salt.

¹H NMR (DMSO-d6) δ7.87-7.94 (m, 6H), 7.48-7.55 (m, 3H), 7.12 (d, 2H, J=9Hz), 4.51 (s, 2H), 4.14 (t, 2H, J=6Hz), 3.20 (t, 2H, 8 Hz), 2.74 (s, 6H), 2.11-2.20 (m, 2H). IR (KBr, cm⁻¹) 3442, 2954, 2673, 2614, 2476, 1616, 1588, 1501, 1477, 1254, 1178, 1254, 1178, 836, 784, 739, 490. MS (ES⁺) m/e 388. Mp(°C)=192.

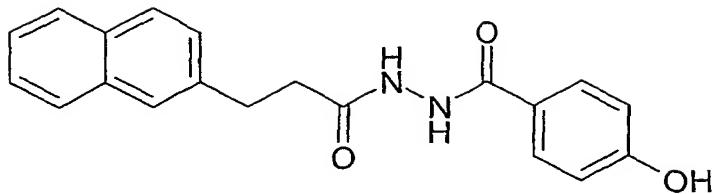
Example 205

Preparation of Dimethyl-{3-[4-(5-naphthalene-2-ylethyl-[1,3,4]oxadiazol-2-yl)phenoxy] propyl}amine



- a) 4-Hydroxybenzoic acid *N*-(3-naphthalen-2-yl-propionyl)hydrazide

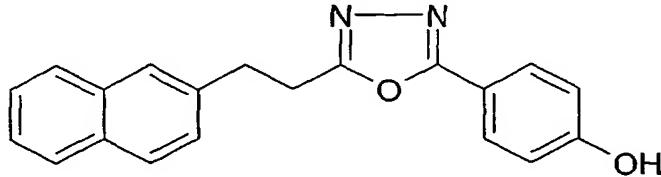
-385-



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 26b, from 3-naphthalen-2-yl propionic acid (1.00 g, 5.0 mmol), 1,1'-carbonyldiimidazole (0.810 g, 5.0 mmol) and 4-hydroxybenzoic hydrazide (0.760 g, 5.0 mmol) to afford an oil that crystallizes out. This material was triturated in EtOAc, filtered to afford 0.320 g (10%) of 4-hydroxybenzoic acid *N*-(3-naphthalen-2-yl-propionyl)hydrazide along with an impurity.

¹H NMR (DMSO-d₆) δ7.76-7.90 (m, 6H), 7.40-7.50 (m, 3H), 7.15-7.20 (m, 2H), 3.14-3.18 (m, 2H), 2.56-2.65 (m, 2H). MS (ES⁺) m/e 333.

10 b) 4-[5-(2-Naphthalen-2-yl-ethyl)-[1,3,4]oxadizol-2-yl]phenol

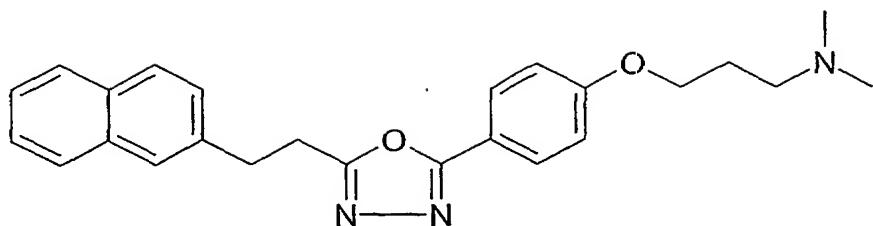


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19d, from 4-hydroxybenzoic acid *N*-(3-naphthalen-2-yl-propionyl)hydrazide (0.320 g, 1.0 mmol), triphenylphosphine (0.502 g, 2.0 mmol), triethylamine (0.310 g, 3.1 mmol) and carbon tetrabromide (0.635 g, 2.0 mmol). Purification by normal phase silica gel radial chromatography (eluted with 3:1 EtOAc:hexane) followed by crystallization from EtOAc afforded 0.277 g (91%) of 4-[5-(2-Naphthalen-2-yl-ethyl)-[1,3,4]oxadizol-2-yl]phenol.

20 ¹H NMR (DMSO-d₆) δ10.26 (bs, 1H), 7.73-7.88 (m, 6H), 7.43-7.51 (m, 3H), 6.91 (d, 2H, J=8Hz), 3.23-3.36 (m, 4H). IR (KBr, cm⁻¹) 3051, 3016, 1603, 1579, 1505, 1443, 1282, 1239, 1170. MS (ES⁺) m/e 317, MS (ES⁻) m/e 315. Anal. Calcd for C₂₀H₁₆N₂O₂ C, 75.93; H, 5.10; N, 8.85. Found C, 75.60; H, 5.14; N, 8.70.

25 d) Dimethyl-{3-[4-(5-naphthalene-2-ylethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl}- amine

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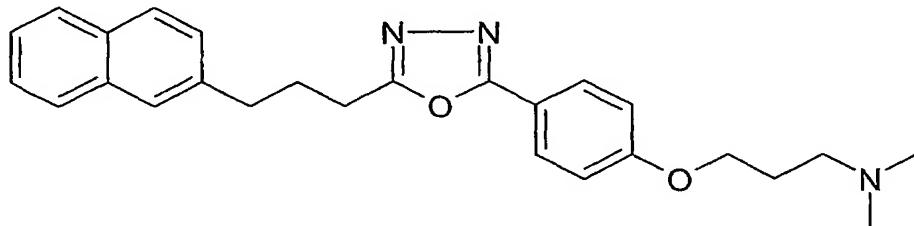


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19e, from 4-[5-(2-Naphthalen-2-yl-ethyl)-[1,3,4]oxadizol-2-yl]phenol (0.388 g, 1.1 mmol), sodium hydride (0.085g, 2.1 mmol) and 3-chloro-N,N-dimethylpropyl amine HCl (0.169g, 1.1 mmol). Purification by radial chromatography on silica gel (eluted with 9:1 Et₂O: 2M NH₃ in MeOH) followed by conversion to the HCl salt as described in Example 5 using the acetyl chloride/EtOH method to generate HCl *in situ* afforded 0.192 g (36%) of dimethyl-{3-[4-(5-naphthalene-2-ylethyl)-[1,3,4]oxadiazol-2-yl]phenoxy} propyl amine as the hydrochloride salt.

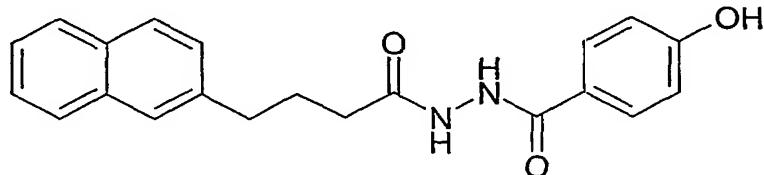
¹H NMR (DMSO-d6) δ7.79-7.91 (m, 6H), 7.43-7.51 (m, 3H), 7.13 (d, 2H, J=9 Hz), 4.16 (t, 2H, J=6 Hz), 3.18-3.38 (m, 6H), 2.76 (s, 6H), 2.12-2.21 (m, 2H). IR(CHCl₃, cm⁻¹) 2969, 1615, 1501, 1475, 1253, 1176. MS (ES⁺) m/e 402. Mp(°C)=208-210.

Example 206

Preparation of dimethyl-{3-[4-(5-naphthalene-2-ylpropyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl amine



a) 4-Hydroxybenzoic acid *N*-(4-naphthalen-2-ylbutyryl)hydrazide



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19c, from 2-naphthalenebutanoic acid (0.600 g, 2.8 mmol), 2-

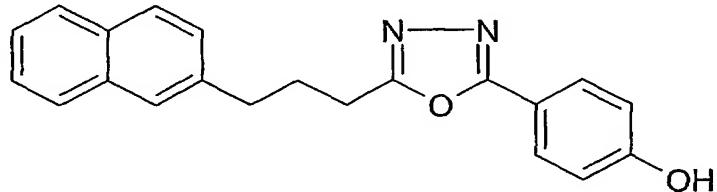
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ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (0.692 g, 2.8 mmol) and 4-hydroxybenzoic hydrazide (0.426 g, 2.8 mmol). Crystallization of the isolated crude material from acetone afforded 0.507 g (52%) of 4-Hydroxybenzoic acid *N*-(4-naphthalen-2-yl-butyryl)hydrazide.

5 ¹H NMR (DMSO-d6) δ10.11 (bd, 2H), 9.74 (bs, 1H), 7.84-7.89 (m, 3H), 7.70-7.77 (m, 3H), 7.35-7.50 (m, 3H), 6.81 (d, 2H, J=8 Hz), 2.81 (t, 2H, J=7 Hz), 2.23 (t, 2H, J=7 Hz), 1.93-2.00 (m, 2H). IR (KBr, cm⁻¹) 3312, 3270, 3015, 1662, 1624, 1608, 1504, 1321, 1279, 1228, 849, 664, 475. MS (ES⁺) m/e 347. Anal. Calcd for C₂₁H₂₀N₂O₃ C, 72.40; H, 5.79; N, 8.04. Found C, 72.04; H, 5.65; N, 7.92.

10

b) 4-[5-(3-Naphthalen-2-yl-propyl)-[1,3,4]oxadiazol-2-yl]phenol

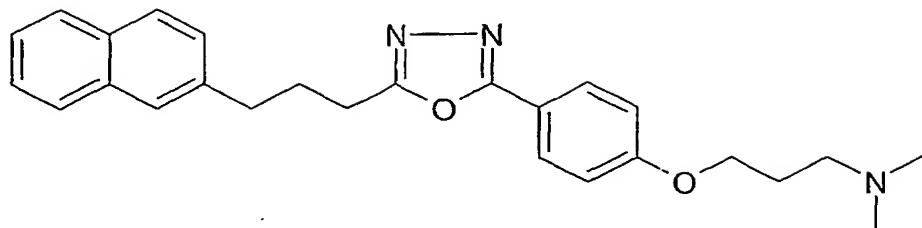


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19d, from 4-hydroxybenzoic acid *N*-(4-naphthalen-2-ylbutyryl)hydrazide (0.464 g, 1.3 mmol), triphenylphosphine (0.699 g, 2.7 mmol), triethylamine (0.270 g, 2.7 mmol) and carbon tetrabromide (0.883 g, 2.7 mmol). Purification by normal phase silica gel radial chromatography (eluted with EtOAc) afforded 4-[5-(3-naphthalen-2-yl-propyl)-[1,3,4]oxadiazol-2-yl]phenol as a solid.

15 ¹H NMR (DMSO-d6) δ10.25 (bs, 1H), 7.72-7.88 (m, 6H), 7.41-7.51 (m, 3H), 6.92 (d, 2H, J=9Hz), 2.86-2.96 (m, 4H), 2.11-2.21 (m, 2H). IR (KBr, cm⁻¹) 1613, 1600, 1502, 1285, 1236, 1175, 856, 820, 746, 473. MS (ES⁺) m/e 331, MS (ES⁻) m/e 329.

c) Dimethyl-{3-[4-(5-naphthalene-2-ylpropyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}propyl}amine

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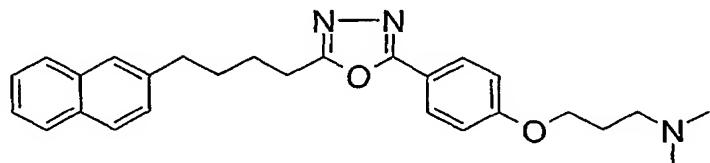
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 21e, from 4-[5-(3-naphthalen-2-yl-propyl)-[1,3,4]oxadiazol-2-yl]phenol (0.252 g, 0.8 mmol), cesium carbonate (0.497 g, 1.5 mmol), and 3-chloro-N,N-dimethylpropylamine HCl (0.121 g, 0.8 mmol). Purification by normal phase silica gel radial chromatography (eluted with 95:5 CHCl₃:2M NH₃ in MeOH) followed by crystallization from Et₂O afforded 0.071 g (22%) of dimethyl-{3-[4-(5-naphthalene-2-ylpropyl)-[1,3,4]oxadiazol-2-yl]- phenoxy}propyl} amine.

¹H NMR (DMSO-d6) δ7.84-7.89 (m, 5H), 7.74 (s, 1H), 7.42-7.51 (m, 3H), 7.10 (d, 2H, J=9Hz), 4.08 (t, 2H, J=6Hz), 2.86-2.98 (m, 4H), 2.36 (t, 2H, J=7Hz), 2.11-2.20 (m, 8H), 1.82-1.91 (m, 2H). IR (KBr, cm⁻¹) 2950, 2817, 2768, 1916, 1587, 1503, 1255, 1172, 1004, 845, 744. MS (ES⁺) m/e 416.. Anal. Calcd for C₂₆H₂₉N₃O₂ C, 75.15; H, 7.03; N, 10.11. Found C, 75.01; H, 6.89; N, 10.02, Mp(°C)=92.

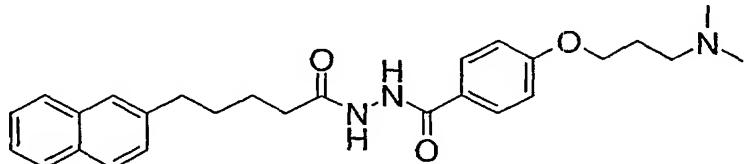
15

Example 207

Preparation of dimethyl-{3-[4-(5-naphthalene-2-ylbutyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl} amine



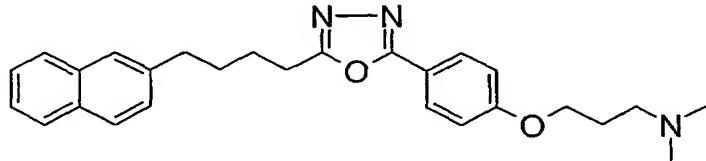
a) 4-(3-Dimethylaminopropoxy)benzoic acid N-(5-naphthalen-2-ylpentanoyl)hydrazide



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 204a, from 2-naphthalenepentanoic acid (0.600 g, 2.6 mmol), 1,1'-carbonyldiimidazole (0.426 g, 2.6 mmol) and 4-[(3-dimethylamino)propoxy]-benzoic acid hydrazide (0.624 g, 2.6 mmol). The reaction suspension was filtered to afford 0.417 g
5 (35%) of 4-(3-Dimethylaminopropoxy)benzoic acid *N*-(5-naphthalen-2-ylpentanoyl)hydrazide.

¹H NMR (DMSO-d₆) δ10.04 (bs, 1H), 9.74 (bs, 1H), 7.79-7.88 (m, 5H), 7.71 (s, 1H), 7.38-7.50 (m, 3H), 6.99 (d, 2H, J=9Hz), 4.05 (t, 2H, J=6Hz), 2.78 (t, 2H, J=7Hz), 2.34 (t, 2H, J=7Hz), 2.23 (t, 2H, J=7Hz), 2.13 (s, 6H), 1.81-1.89 (m, 2H), 1.58-1.76 (m, 10 4H). IR (KBr, cm⁻¹) 3203, 2935, 2855, 2762, 1665, 1598, 1568, 1465, 1256, 1173, 843, 818, 474. MS (ES⁺) m/e 448, MS (ES⁻) m/e 446. Anal. Calcd for C₂₇H₃₃N₃O₃ C, 72.46; H, 7.43; N, 9.39. Found C, 72.51; H, 7.46; N, 9.20.

b) Dimethyl-{3-[4-(5-naphthalene-2-ylbutyl)-[1,3,4]oxadiazol-2-yl]phenoxy} propyl}- amine
15



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19d, from 4-(3-Dimethylaminopropoxy)benzoic acid *N*-(5-naphthalen-2-ylpentanoyl)hydrazide (0.303 g, 0.68 mmol), triphenylphosphine (0.355 g, 20 1.4 mmol), triethylamine (0.137 g, 1.4 mmol) and carbon tetrabromide (0.449 g, 1.4 mmol). Purification by normal phase silica gel chromatography (eluted with 9:1 CHCl₃:2M NH₃ in MeOH) followed by conversion to the HCl salt, as described in Example 5 using the acetyl chloride/EtOH method to generate HCl *in situ*, afforded the title compound. Crystallization from Et₂O:MeOH afforded 0.080 g (7%) of dimethyl-{3-[4-(5-naphthalene-2-ylbutyl)-[1,3,4]oxadiazol-2-yl]phenoxy} propyl amine.
25

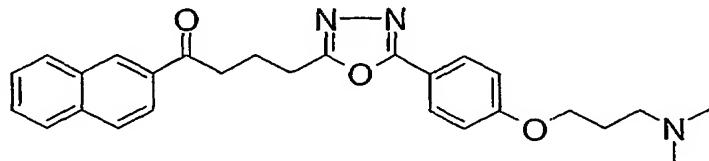
¹H NMR (DMSO-d₆) δ 7.82-7.92 (m, 5H), 7.70 (s, 1H), 7.38-7.50 (m, 3H), 7.11 (d, 2H, J=9Hz), 4.15 (t, 2H, J=6Hz), 3.21 (t, 2H, J=8Hz), 2.94-2.99 (m, 2H), 2.76-2.84 (m,

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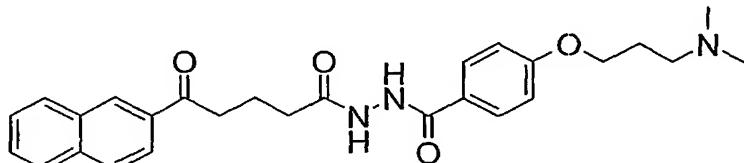
8H), 2.12-2.21 (m, 2H), 1.79-1.81 (m, 4H). IR (KBr, cm⁻¹) 2936, 1613, 1502, 1256, 1256, 1175. MS (ES⁺) m/e 430. Mp(°C)=195.

Example 208

- 5 Preparation of 4-{5-[4-(3-Dimethylaminopropoxy)phenyl]-[1,3,4]oxadiazol-2yl}-1-naphthalen-2yl-butan-1-one



- a) 4-(3-Dimethylaminopropoxy)benzoic acid N-(5-naphthalen-2-yl-5-oxopentanoyl)hydrazide

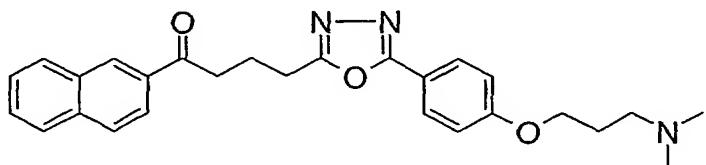


10

The above compound was prepared in a manner similar to that exemplified for the preparation of Example 204a, from 4-(2-naphthoyl)butyric acid (0.705 g, 2.9 mmol), 1,1'-carbonyldiimidazole (0.472 g, 2.9 mmol) and 4-[(3-dimethylamino)propoxy]-benzoic acid hydrazide (0.691 g, 2.9 mmol). After stirring 6.5 hours at room temperature the reaction mixture was concentrated to an oil. The oil was treated with 25 ml each of EtOAc and H₂O. Crystals that formed in this mixture were collected by filtration to afford 0.536 g (40%) of the title compound. The filtrate was concentrated to a solid. Purification by normal phase silica gel radial chromatography (eluted with 9:1 CHCl₃:2M NH₃ in MeOH) afforded 0.120 g (9%) of the title compound. 0.656 g (49%) of 4-(3-dimethylaminopropoxy)benzoic acid N-(5-naphthalen-2-yl-5-oxopentanoyl)hydrazide was collected.

¹H NMR (DMSO-d6) δ10.15 (bs, 1H), 9.84 (bs, 1H), 8.72 (s, 1HY), 8.13 (m, 1H), 7.97-8.06 (m, 3H), 7.84 (d, 2H, J=9Hz), 7.60-7.70 (m, 2H), 7.00 (d, 2H, J=9Hz), 4.06 (t, 2H, J=6Hz), 3.26-3.32 (m, 2H), 2.30-2.37 (m, 4H), 2.11 (s, 6H), 1.93-2.02 (m, 2H), 1.81-1.88 (m, 2H). IR (KBr, cm⁻¹) 3422, 3252, 2949, 2792, 1683, 1644, 1604, 1504, 1468, 1251, 1178, 1122, 758. MS (ES⁺) m/e 462, MS (ES⁻) m/e 460.

b) 4-{5-[4-(3-Dimethylaminopropoxy)phenyl]-[1,3,4]oxadiazol-2yl}-1-naphthalen-2yl-butan-1-one

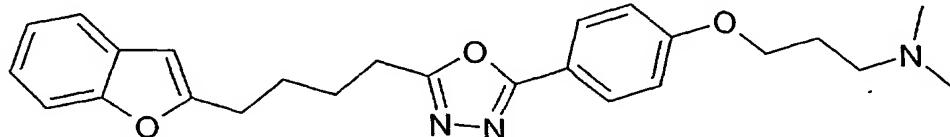


5 The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19d, from 4-(3-dimethylaminopropoxy)benzoic acid N-(5-naphthalen-2-yl-5-oxopentanoyl)hydrazide (0.334 g, 0.72 mmol), triphenylphosphine (0.380 g, 1.5 mmol), triethylamine (0.146 g, 1.5 mmol) and carbon tetrabromide (0.480 g, 1.5 mmol). Purification by normal phase silica gel chromatography (eluted with 9:1
10 CHCl₃:2M NH₃ in MeOH) followed by conversion to the HCl salt, as described in Example 5 using the acetyl chloride/EtOH method to generate HCl *in situ*, afforded 0.119 g (34%) of 4-{5-[4-(3-dimethylaminopropoxy)- phenyl]-[1,3,4]oxadiazol-2yl}-1-naphthalen-2yl-butan-1-one.

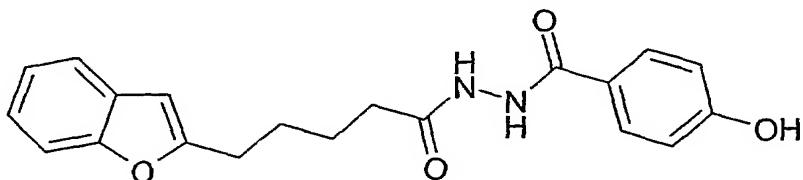
15 ¹H NMR (DMSO-d6) δ8.68 (s, 1H), 8.12 (d, 1H, J=7Hz), 7.97-8.06 (m, 3H), 7.90 (d, 2H, J=9Hz), 7.60-7.71 (m, 2H), 7.10 (d, 2H, J=9Hz), 4.15 (t, 2H, J=6Hz), 3.37 (t, 2H, J=7Hz), 3.21 (t, 2H, J=8Hz), 3.05 (t, 2H, J=7 Hz), 2.76 (s, 6H), 2.13-2.24 (m, 4H). IR (CHCl₃, cm⁻¹) 2969, 1681, 1615, 1501, 1254, 1176. MS (ES⁺) m/e 444. Mp(°C)=211.

Example 209

20 Preparation of (3-{4-[5-Benzofuran-2-ylbutyl]-[1,3,4]oxadiazol-2-yl]phenoxy}-propyl)dimethylamine



a) 4-Hydroxybenzoic acid N-(5-benzofuran-2-yl pentanoyl)hydrazide

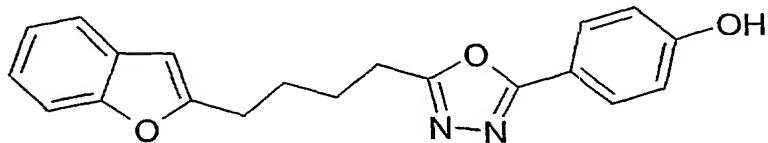


-392-

The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19c, from 5-benzofuran-2-yl-pentanoic acid (2.04 g, 9.3 mmol), 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (2.31 g, 9.3 mmol) and 4-hydroxybenzoic hydrazide (1.42 g, 9.3 mmol). Purification by normal phase silica gel chromatography (eluted with linear gradient of 2 to 10% 2M NH₃ in MeOH:CH₂Cl₂) to afford 1.77 g (54%) of 4-hydroxybenzoic acid *N*-(5-benzofuran-2-yl pentanoyl)hydrazide as a foam.

¹H NMR (DMSO-d6) δ10.06 (bs, 1H), 10.00 (bs, 1H), 9.74 (s, 1H), 7.73 (d, 2H, J=9Hz), 7.45-7.56 (m, 2H), 7.15-7.24 (m, 2H), 6.80 (d, 2H, J=9Hz), 6.60 (s, 1H), 2.78-2.83 (m, 2H), 2.23 (t, 2H, J=7Hz), 1.59-1.80 (m, 4H). IR (KBr, cm⁻¹) 3238, 2945, 1686, 1643, 608, 1586, 1503, 1455, 1310, 1253, 1173, 752. MS (ES⁺) m/e 353, MS (ES⁻) m/e 351.

b) 4-{5-[4-Benzofuran-2-ylbutyl]-[1,3,4]oxadiazol-2-yl}phenol
15

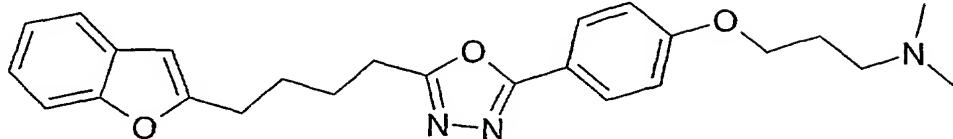


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19d, from 4-hydroxybenzoic acid *N*-(5-benzo-furan-2-yl pentanoyl)hydrazide (1.63 g, 4.6 mmol), triphenylphosphine (2.43 g, 9.3 mmol), imidazole (1.01g, 14.8 mmol) and carbon tetrabromide (3.07 g, 9.3 mmol). Purification by normal phase silica gel chromatography (eluted with 1:1 EtOAc:hexane) followed by crystallization from acetone afforded 0.479 g (31%) of 4-{5-[4-Benzofuran-2-ylbutyl]-[1,3,4]oxadiazol-2-yl}phenol.

¹H NMR (DMSO-d6) δ10.26 (bs, 1H), 7.77 (d, 2H, J=8Hz), 7.45-7.55 (m, 2H), 6.92 (d, 2H, J=8Hz), 6.61 (s, 1H), 2.96 (t, 2H, J=7Hz), 2.84 (t, 2H, J=6Hz), 1.76-1.89 (m, 4H). IR (KBr, cm⁻¹) 1616, 1600, 1582, 1447, 1280, 1250, 837, 752, 740. MS (ES⁺) m/e 335, MS (ES⁻) m/e 333. Anal. Calcd for C₂₀H₁₈N₂O₃ C, 71.84; H, 5.43; N, 8.38. Found C, 71.95; H, 5.47; N, 8.41.

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- c) (3-{4-[5-Benzofuran-2-ylbutyl]-[1,3,4]oxadiazol-2-yl}phenoxy}propyl)dimethylamine

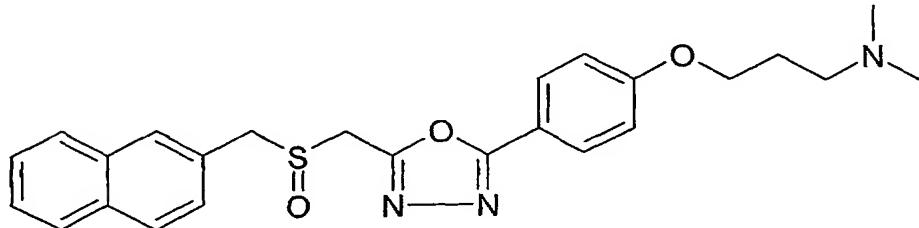


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19e, from 4-{5-[4-Benzofuran-2-ylbutyl]-[1,3,4]oxadiazol-2-yl}phenol (0.669 g, 2.0 mmol), sodium hydride (0.160g, 4.0 mmol) and 3-chloro-N,N-dimethylpropyl amine HCl (0.316g, 2.0 mmol). Purification by radial chromatography on silica gel (eluted with 9:1 Et₂O: 2M NH₃ in MeOH) followed by conversion to the HCl salt as described in Example 5 using the acetyl chloride/EtOH method to generate HCl *in situ* afforded 0.132 g (14%) of (3-{4-[5-Benzofuran-2-ylbutyl]-[1,3,4]oxadiazol-2-yl}phenoxy}propyl)dimethylamine as the hydrochloride salt.

¹H NMR (DMSO-d6) δ7.90 (d, 2H, J=9Hz), 7.40-7.54 (m, 2H), 7.11-7.24 (m, 4H), 6.61 (s, 1H), 4.16 (t, 2H, J=6Hz), 3.21 (t, 2H, J=8Hz), 2.98 (t, 2H, J=7Hz), 2.85 (t, 2H, J=7Hz), 2.78 (s, 6H), 2.12-2.22 (m, 2H), 1.80-1.99 (m, 4H). IR (CHCl₃, cm⁻¹) 2967, 1615, 1501, 1474, 1455, 1253, 1176. MS (ES⁺) m/e 420. Analytical HPLC: 100%. Mp(°C)=200.

Example 210

Preparation of Dimethyl-(3-{4-[5-(naphthalene-2-ylmethanesulfinylmethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)amine



To a solution of dimethyl(3-{4-[5-naphthalen-2-ylmethysulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)amine (0.187 g, 0.4 mmol) in 4 ml CH₂Cl₂ at room temperature was added acetic acid (5.18 g, 86.2 mmol) and m-chloroperbenzoic acid (0.074g, 0.4 mmol). After stirring thirty minutes the reaction was quenched with Na₂SO₃.

The mixture was diluted with H₂O then extracted twice with EtOAc. Purification by normal phase silica gel radial chromatography (eluted with 95:5 CHCl₃:2M NH₃ in MeOH) followed by conversion to the HCl salt as described in Example 5 using the acetyl chloride/EtOH method to generate HCl *in situ* afforded 0.062 g (30%) of dimethyl-(3-{4-[5-(naphthalene-2-ylmethanesulfonylmethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)amine.

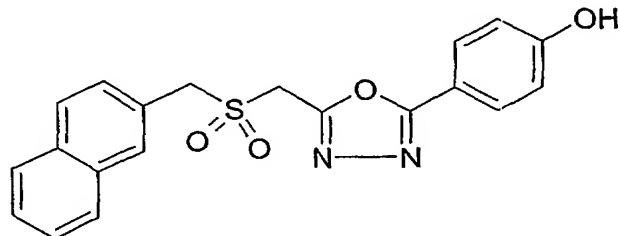
¹H NMR (DMSO-d₆) δ7.89-7.97 (m, 6H), 7.53-7.56 (m, 3H), 7.15 (d, 2H, J=9 Hz), 4.60-4.77 (m, 2H), 4.36-4.48 (m, 2H), 4.17 (t, 2H, J=6Hz), 3.19-3.24 (m, 2H), 2.73 (s, 6H), 2.14-2.23 (m, 2H). IR (KBr, cm⁻¹) 3429, 2954, 2601, 2476, 1613, 1498, 1472, 1258, 1177, 1087, 1054, 838, 742. MS (ES⁺) m/e 450. Mp(°C)=183.

Example 211

Preparation of Dimethyl(3-{4-[5-(naphthalene-2-ylmethanesulfonylmethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)amine

15

a) 4-[5-(naphthalene-2-ylmethane- sulfonylmethyl)-[1,3,4]oxadiazol-2-yl]phenol



To a solution of 4-[5-(naphthalene-2-ylmethanesulfonylmethyl)-[1,3,4]oxadiazol-

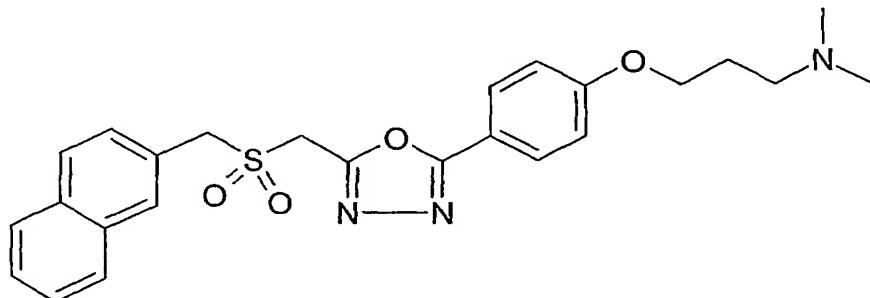
2-yl]phenol (0.690 g, 2.0 mmol) in 5 ml DMF at room temperature was added m-

20 chloperbenzoic acid (1.46 g, 8.5 mmol). The reaction was stirred three hours at room temperature then quenched with aqueous Na₂SO₃. The mixture was reduced in volume then diluted with H₂O and extracted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated to a solid. Crystallization from Et₂O

afforded (0.492 g, 65%) of 4-[5-(naphthalene-2-ylmethanesulfonylmethyl)-[1,3,4]-oxadiazol-2-yl]phenol.

¹H NMR (DMSO-d₆) δ10.37 (bs, 1H), 7.88-8.01 (m, 4H), 7.77 (d, 2H, J=9Hz), 7.52-7.59 (m, 3H), 6.94 (d, 2H, J=9Hz), 5.12 (s, 2H), 4.94 (s, 2H). IR (KBr, cm⁻¹) 2986, 1660, 1614, 1598, 1507, 1498, 1443, 1319, 1284, 1241, 1173, 1137, 1120, 839, 751, 484. MS (ES⁺) m/e 381, MS (ES⁻) m/e 379.

b) Dimethyl(3-{4-[5-(naphthalene-2-ylmethanesulfonylmethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)amine



1.0

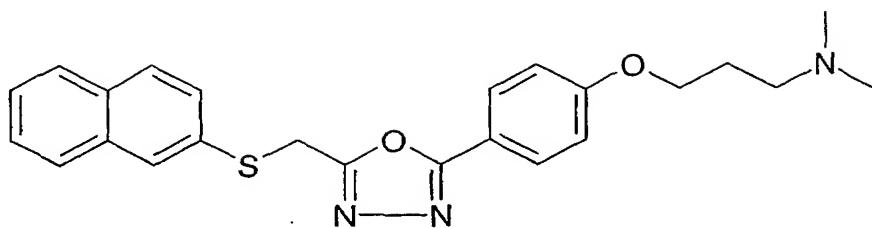
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 21e, from 4-[5-(naphthalene-2-ylmethane- sulfonylmethyl)-[1,3,4]oxadiazol-2-yl]phenol (0.438 g, 1.2 mmol), cesium carbonate (0.750 g, 2.3 mmol), and 3-chloro-N,N-dimethylpropylamine HCl (0.182 g, 1.2 mmol). Purification by normal phase silica gel radial chromatography (eluted with 9:1 CHCl₃:2M NH₃ in MeOH) followed by treatment with oxalic acid afforded 0.17 mg (3%) of dimethyl(3-{4-[5-(naphthalene-2-ylmethanesulfonylmethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)amine as the oxalate salt.

¹H NMR (DMSO-d₆) δ8.01-7.85 (m, 6H), 7.60-7.51 (m, 3H), 7.15-7.20 (m, 2H), 5.14 (s, 2H), 4.93 (s, 2H), 4.10-4.18 (m, 2H), 3.13-3.20 (m, 2H), 2.76 9 (s, 6H), 2.18-2.08 (m, 2H). IR (KBr, cm⁻¹) 1614, 1501, 1312, 1260, 1181, 1141, 844, 707, 484. MS (ES⁺) m/e 466. Mp(°C)=218.

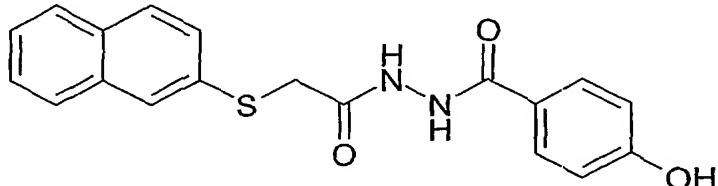
Example 212

25 Preparation of Dimethyl(3-{4-[5-naphthalen-2-ylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)amine

-396-



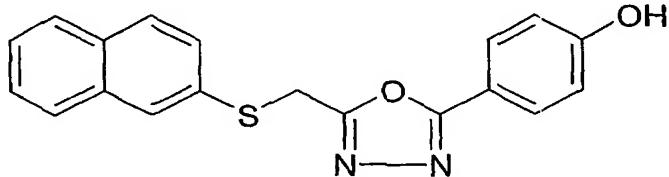
- a) 4-hydroxybenzoic acid *N*-[2-(naphthalene-2-ylsulfanyl)acetyl]hydrazide



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 26b, from 2-naphthylmercapto acetic acid (1.50 g, 6.9 mmol), 1,1'-carbonyldiimidazole (1.11 g, 6.9 mmol) and 4-hydroxybenzoic hydrazide (1.05 g, 6.9 mmol). Crystallization of the crude material from EtOAc afforded 1.95 g (81%) of 4-hydroxybenzoic acid *N*-[2-(naphthalene-2-ylsulfanyl)acetyl]hydrazide.

¹H NMR (DMSO-d₆) δ 10.21 (bs, 2H), 10.08 (bs, 1H), 7.95 (s, 1H), 7.85-7.89 (m, 3H), 7.75 (d, 2H, J=9Hz), 7.42-7.55 (m, 3H), 6.82 (d, 2H, J=9Hz), 3.89 (s, 2H). IR (KBr, cm⁻¹) 3314, 3213, 3006, 1703, 1621, 1605, 1584, 1516, 1282, 1228, 1175, 847, 810, 746, 478. MS (ES⁺) m/e 353, MS (ES⁻) m/e 351.

- b) 4-[5-naphthalen-2-ylsulfanyl methyl]-[1,3,4]oxadiazol-2-yl]phenol



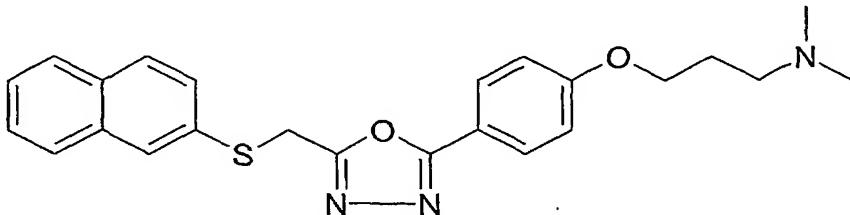
15

The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19d, from 4-hydroxybenzoic acid *N*-[2-(naphthalene-2-ylsulfanyl)acetyl]hydrazide (1.81 g, 5.1 mmol), triphenylphosphine (2.69 g, 10.3 mmol), triethylamine (1.87g, 18.5 mmol) and carbon tetrabromide (3.41 g, 10.3 mmol).

20 Purification by normal phase silica gel chromatography (eluted with 8:1 EtOAc:hexane) followed by crystallization from acetone afforded 0.885 g (51%) of 4-[5-naphthalen-2-ylsulfanyl methyl]-[1,3,4]oxadiazol-2-yl]phenol.

¹H NMR (DMSO-d₆) δ10.29 (bs, 1H), 8.02 (s, 1H), 7.90 (d, 2H, J=9Hz), 7.83-7.86 (m, 1H), 7.64 (d, 2H, J=9Hz), 7.48-7.60 (m, 3H), 6.86 (d, 2H, J=9Hz), 4.62 (s, 2H). IR (KBr, cm⁻¹) 1614, 1561, 1497, 1291, 1225, 1175, 1083, 1020, 819, 758, 478. MS (ES⁺) m/e 335. Anal. Calcd for C₁₉H₁₄N₂O₂S C, 68.25; H, 4.22; N, 8.38. Found C, 68.10; H, 4.02; N, 8.25.

c) Dimethyl(3-{4-[5-naphthalen-2-ylsulfanylmethyl]-[1,3,4]oxadiazol-2-yl}phenoxy}propyl)amine

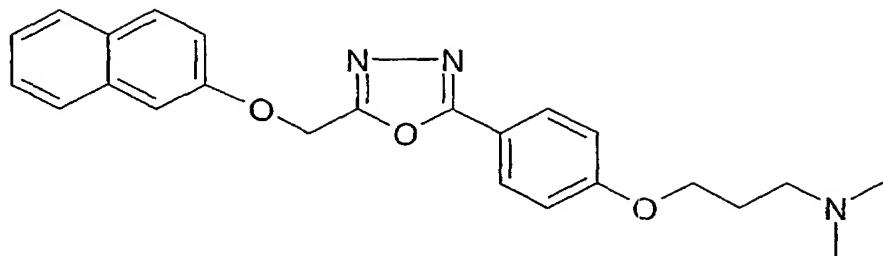


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19e, from 4-[5-naphthalen-2-ylsulfanylmethyl]-[1,3,4]oxadiazol-2-yl]phenol (0.800 g, 2.4 mmol), sodium hydride (0.196g, 4.9 mmol) and 3-chloro-N,N-dimethylpropyl amine HCl (0.378g, 2.4 mmol). Purification by radial chromatography on silica gel (eluted with 9:1 CHCl₃: 2M NH₃ in MeOH) followed by crystallization from Et₂O:MeOH afforded 0.204g (20%) of dimethyl(3-{4-[5-naphthalen-2-ylsulfanylmethyl]-[1,3,4]oxadiazol-2-yl}phenoxy}propyl)amine.

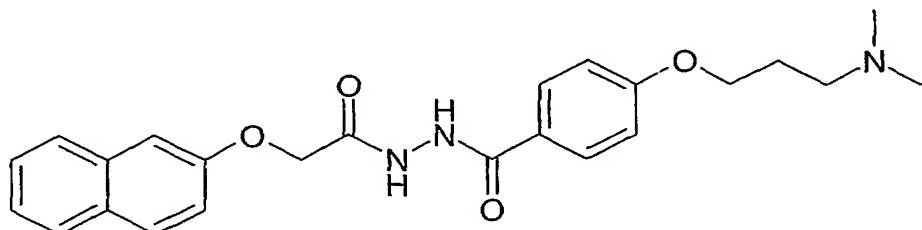
¹H NMR (DMSO-d₆) δ8.02 (s, 1H), 7.90 (d, 2H, J=9Hz), 7.83-7.88 (m, 1H), 7.74 (d, 2H, J=9Hz), 7.49-7.60 (m, 3H), 7.05 (d, 2H, J=9Hz), 4.87 (s, 2H), 4.06 (t, 2H, J=6Hz), 2.34 (t, 2H, J=7Hz), 2.10 (s, 6H), 1.81-1.90 (m, 2H). IR (KBr, cm⁻¹) 1607, 1502, 1469, 1299, 1255, 1179, 954, 817, 752, 659, 471. MS (ES⁺) m/e 420. Anal. Calcd for C₂₄H₂₅N₃O₂S C, 68.71; H, 6.01; N, 10.02. Found C, 68.45; H, 5.87; N, 9.89. Mp(°C)=106.

Example 213

Preparation of dimethyl(3-{4-[5-naphthalen-2-yloxymethyl]-[1,3,4]oxadiazol-2-yl}phenoxy}propyl)amine



- a) 4-(3-dimethylaminopropoxy)benzoic acid *N*-[2-(naphthalene-2-yloxy)acetyl]hydrazide



5

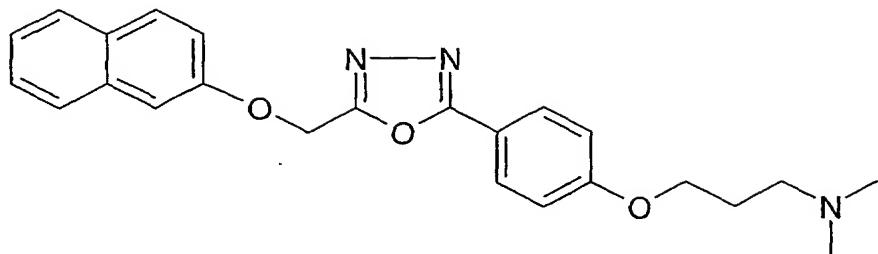
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 204a, from (2-naphthoxy)acetic acid (0.285 g, 1.4 mmol), 1,1'-carbonyldiimidazole (0.228 g, 1.4 mmol) and 4-[(3-dimethylamino)propoxy]-benzoic acid hydrazide (0.334 g, 1.4 mmol). After stirring at room temperature for 24 hours, the

10 insolubles were collected by filtration to afford (0.373 g, 63%) of 4-(3-dimethylaminopropoxy)benzoic acid *N*-[2-(naphthalene-2-yloxy)acetyl]hydrazide.

15 ¹H NMR (DMSO-d₆) δ10.26 (bs, 2H), 7.80-7.88 (m, 5H), 7.27-7.51 (m, 4H), 7.01 (d, 2H, J=9Hz), 4.78 (s, 2H), 4.07 (t, 2H, J=6Hz), 2.37 (t, 2H, J=7Hz), 2.15 (s, 6H), 1.82-1.91 (m, 2H). IR (KBr, cm⁻¹) 3212, 3058, 2955, 2829, 2777, 1685, 1652, 1607, 1512, 1313, 1260, 1183, 851, 809, 745, 473. MS (ES⁺) m/e 422, MS (ES⁻) m/e 420.

- b) Dimethyl(3-{4-[5-naphthalen-2-yloxymethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)amine.

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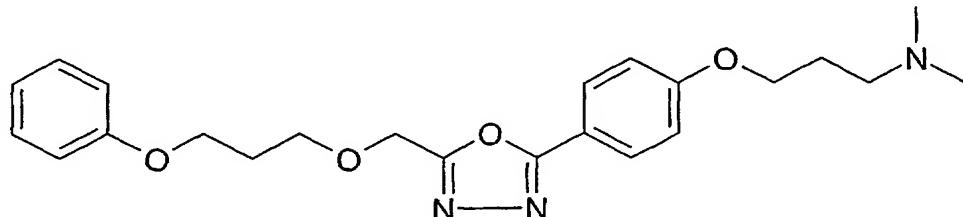


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19d, from 4-(3-dimethylaminopropoxy)benzoic acid *N*-[2-(naphthalene-2-yloxy)acetyl]hydrazide (0.322 g, 0.8 mmol), triphenyl -phosphine (0.401 g, 1.5 mmol), triethylamine (0.247 g, 2.4 mmol) and carbon tetra- bromide (0.507 g, 1.5 mmol). Purification by normal phase silica gel chromatography (eluted with 9:1 CH₂Cl₂:2M NH₃ in MeOH) followed by conversion to the HCl salt, as described in Example 5 using the acetyl chloride/EtOH method to generate HCl *in situ*, afforded 0.136 g (40%) of dmethyl(3-{4-[5-naphthalen-2-yloxymethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)amine as the hydrochloride salt.

¹H NMR (DMSO-d6) δ7.97 (d, 2H, J=9 Hz), 7.82-7.91 (m, 3H), 7.56 (d, 1H, J=3 Hz), 7.50 (t, 1H, J=8Hz), 7.40 (T, 1H, J=8Hz), 7.29 (dd, 1H, J = 3, 9Hz), 7.15 (d, 2H, J=9 Hz), 5.59 (s, 2H), 4.17 (t, 2H, J=6Hz), 3.21 (t, 2H, J=8Hz), 2.78 (s, 6H), 2.12-2.21 (m 2H). IR (KBr, cm⁻¹) 2947, 2555, 2503, 2406, 1618, 1500, 1467, 1393, 1247, 1209, 1178, 1116, 1059, 1012, 957, 839, 805, 749, 472. MS (ES⁺) m/e 404. Analytical HPLC:100%. Mp(°C)=Decomposes at 186.

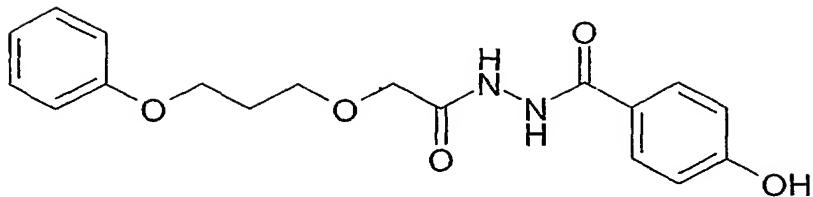
Example 214

Preparation of Dimethyl-(3-{4-{5-(3-phenoxypropoxymethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)amine.



- a) 4-hydroxybenzoic acid *N*-[2-(3-phenoxypropoxy)acetyl]hydrazide

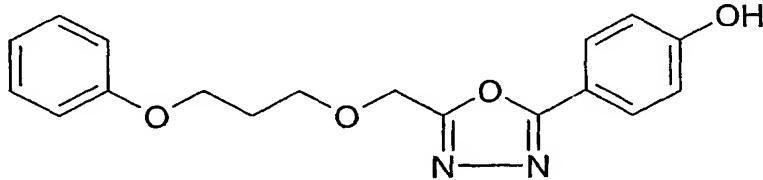
-400-



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19c, from (3-phenoxypropoxy)acetic acid (2.70 g, 12.8 mmol), 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (3.18 g, 12.8 mmol) and 4-hydroxybenzoic hydrazide (1.95 g, 12.8 mmol). The resultant crystalline material that formed in the reaction mixture was collected by filtration to afford 2.42 g (55%) of 4-hydroxybenzoic acid *N*-[2-(3-phenoxypropoxy)acetyl]hydrazide.

¹H NMR (DMSO-d₆) δ10.06 (bs, 2H), 9.73 (bs, 1H), 7.74 (d, 2H, J=9Hz), 7.24-7.31 (m, 2H), 6.89-6.95 (m, 3H), 6.81 (d, 2H, J=9Hz), 4.08 (t, 2H, J=6Hz), 4.02 (s, 2H), 3.67 (t, 2H, J=6Hz), 1.98-2.06 (m, 2H). IR (KBr, cm⁻¹) 3219, 1686, 1630, 1609, 1498, 1443, 1279, 1242, 1173, 1134, 755. MS (ES⁺) m/e 343. Anal. Calcd for C₁₈H₂₀N₂O₅ C, 62.78; H, 5.85; N, 8.13. Found C, 62.68; H, 5.74; N, 8.01.

b) 4-[-5-(3-Phenoxypropoxymethyl)-[1,3,4]oxadiazol-2-yl]phenol



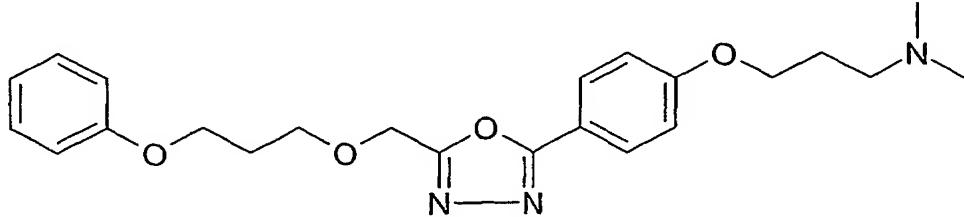
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19d, from of 4-hydroxybenzoic acid *N*-[2-(3-phenoxypropoxy)acetyl]hydrazide (2.07 g, 6.0 mmol), triphenylphosphine (3.15 g, 12.0 mmol), triethylamine (2.19 g, 21.6 mmol) and carbon tetrabromide (3.99 g, 12.0 mmol). Purification by chromatography on silica gel (eluted with 1:1 EtOAc:hexane) afforded 1.65 g (85%) of 4-[-5-(3-Phenoxypropoxymethyl)-[1,3,4]oxadiazol-2-yl]phenol as a solid.

¹H NMR (DMSO-d₆) δ10.32 (bs, 1H), 7.80 (d, 2H, J=9Hz), 7.21-7.28 (m, 2H), 6.88-6.96 (m, 5H), 4.77 (s, 2H), 4.02 (t, 2H, J=6Hz), 3.70 (t, 2H, J=6Hz), 1.95-2.04 (m, 2H). IR (KBr, cm⁻¹) 3101, 2958, 2871, 1609, 1497, 1470, 1285, 1240, 1172, 1087, 757,

-401-

737. MS (ES^+) m/e 327, MS (ES^-) m/e 325. Anal. Calcd for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_4$ C, 66.25; H, 5.56; N, 8.58. Found C, 66.28; H, 5.48; N, 8.54.

- c) Dimethyl-(3-{4-{5-(3-phenoxypropoxymethyl)-[1,3,4]oxadiazol-2-yl} phenoxy} propyl)amine



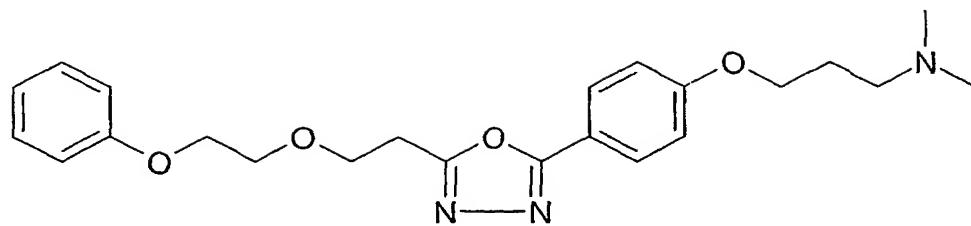
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 21e, from 4-[5-(3-Phenoxypropoxymethyl)-[1,3,4]oxadiazol-2-yl]phenol (1.42 g, 4.4 mmol), cesium carbonate (2.84 g, 8.7 mmol), and 3-chloro-N,N-dimethylpropylamine HCl (0.688 g, 4.4 mmol). Purification by radial chromatography on silica gel (eluted with a linear gradient of 2 to 5% 2M NH_3 in $\text{MeOH}:\text{CHCl}_3$) followed by conversion to the HCl salt, as described in Example 5 using the acetyl chloride/EtOH method to generate HCl *in situ*, afforded 0.311 g (16%) of dimethyl-(3-{4-{5-(3-phenoxypropoxymethyl)-[1,3,4]oxadiazol-2-yl} phenoxy} propyl)amine as the hydrochloride salt.

^1H NMR (DMSO-d6) δ 7.91 (d, 2H, $J=9\text{Hz}$), 7.21-7.27 (m, 2H), 7.13 (d, 2H, $J=9\text{Hz}$), 6.88-6.92 (m, 3H), 4.79 (s, 2H), 4.17 (t, 2H, $J=6\text{Hz}$), 4.03 (t, 2H, $J=6\text{Hz}$), 3.72 (t, 2H, $J=6\text{Hz}$), 3.21 (t, 2H, $J=8\text{Hz}$), 2.78 (s, 6H), 2.14-2.24 (m, 2H), 1.96-2.04 (m, 2H). IR (KBr, cm^{-1}) 2474, 1617, 1602, 1499, 1472, 1257, 1171, 1085, 1052, 751. MS (ES^+) m/e 412. Mp($^\circ\text{C}$)=132.

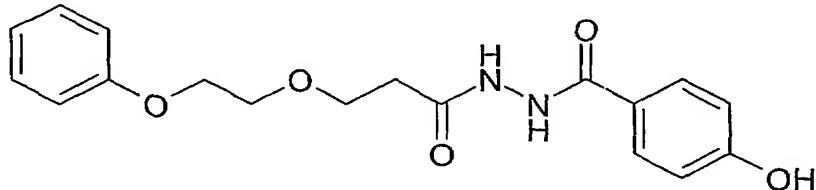
Example 215

Preparation of Dimethyl-[3-(4-{5-[2-(2-phenoxyethoxy)ethyl]-[1,3,4]oxadiazol-2-yl} phenoxy)propyl]amine

-402-



- a) 4-Hydroxybenzoic acid *N'*-(3-(2-phenoxyethoxy)propionyl)hydrazide



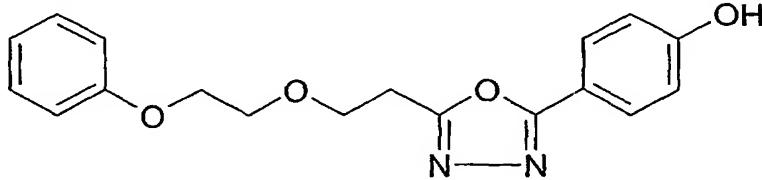
The above compound was prepared in a manner similar to that exemplified for the

5 preparation of Example 19c, from 3-(2-phenoxyethoxy)propionic acid (6.35 g, 30.2 mmol), 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (7.47 g, 30.2 mmol) and 4-hydroxybenzoic hydrazide (4.64 g, 30.2 mmol). Purification by chromatography on silica gel (eluted with a linear gradient of 2 to 5% 2M NH₃ in MeOH:CHCl₃) afforded 4.73 g (70%) of 4-hydroxybenzoic acid *N'*-(3-(2-phenoxyethoxy)propionyl)hydrazide as a foam.

10 ¹H NMR (DMSO-d6) δ10.06 (bs, 2H), 9.82 (bs, 1H), 7.73 (d, 2H, J=9Hz), 7.23-7.31 (m, 2H), 6.87-6.96 (m, 3H), 6.80 (d, 2H, J=8Hz), 4.07 (t, 2H, J=5Hz), 3.64-3.75 (m, 4H), 2.41-2.54 (m, 2H). IR (CHCl₃, cm⁻¹) 3266, 3012, 2930, 2878, 1688, 1646, 1609, 1497, 1456, 1279, 1245, 1225, 1173, 1122, 849. MS (ES⁺) m/e 345, MS (ES⁻) m/e 343.

15

- b) 4-{5-[2-(2-phenoxyethoxy)ethyl]-[1,3,4]oxadiazol-2-yl}phenol



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19d, from of 4-hydroxybenzoic acid *N'*-(3-(2-

20 phenoxyethoxy)propionyl)hydrazide (4.71 g, 13.7 mmol), triphenylphosphine (7.17 g, 27.4 mmol), triethylamine (4.98 g, 49.2 mmol) and carbon tetrabromide (9.07 g, 27.4 mmol). Purification by chromatography on silica gel (eluted with 4:1 EtOAc:hexane)

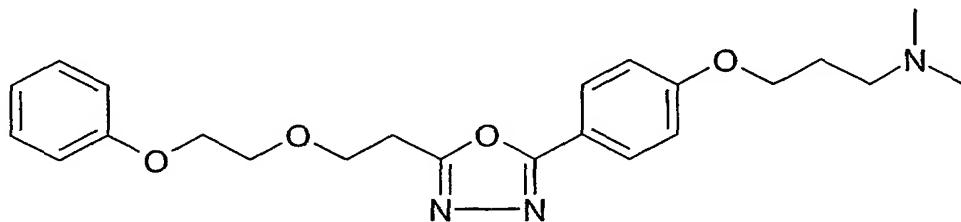
-403-

afforded 4.40 g (99%) of 4-{5-[2-(2-phenoxyethoxy)ethyl]-[1,3,4]oxadiazol-2-yl}phenol as an oil. Product co-eluted with triphenylphosphine.

¹H NMR (DMSO-d₆) δ10.25 (bs, 1H), 7.78 (d, 2H, J=9Hz), 7.21-7.27 (m, 2H), 6.88-6.94 (m, 5H), 4.06-4.08 (m, 2H), 3.91 (t, 2H, J=6Hz), 3.76-3.79 (m, 2H), 3.18(t, 2H, J=6Hz). IR (CHCl₃, cm⁻¹) 3006, 1732, 1615, 1600, 1499, 1438, 1375, 1247, 1171, 1121, 1046. MS (ES⁺) m/e 327, MS (ES⁻) m/e 325.

c) Dimethyl-[3-(4-{5-[2-(2-phenoxyethoxy)ethyl]-[1,3,4]oxadiazol-2-yl}phenoxy)propyl]amine.

10



15

The above compound was prepared in a manner similar to that exemplified for the preparation of Example 21e, from 4-{5-[2-(2-phenoxyethoxy)ethyl]-[1,3,4]oxadiazol-2-yl}phenol (2.02 g, 6.1 mmol), cesium carbonate (3.98 g, 12.2 mmol), and 3-chloro-N,N-dimethylpropylamine HCl (0.966 g, 6.1 mmol). Purification by chromatography on silica gel (eluted with a linear gradient of 2 to 10% 2M NH₃ in MeOH:CHCl₃) followed by conversion to the oxalate salt afforded 0.053 g (2%) of dimethyl-[3-(4-{5-[2-(2-phenoxyethoxy)ethyl]-[1,3,4]oxadiazol-2-yl}phenoxy)propyl]amine as the oxalate salt.

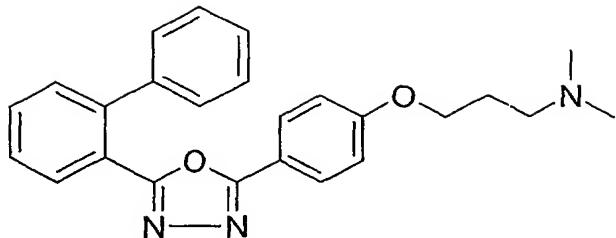
20

¹H NMR (DMSO-d₆) δ7.90 (d, 2H, J=9Hz), 7.22-7.27 (m, 2H), 7.12 (d, 2H, J=9Hz), 6.88-6.93 (m, 3H), 4.14 (t, 2H, J=6Hz), 4.05-4.09 (m, 2H), 3.92 (t, 2H, J=6Hz), 3.77-3.80 (m, 2H), 3.14-3.22 (m, 4H), 2.76 (s, 6H), 2.08-2.17 (m, 2H). IR (KBr, cm⁻¹) 1725, 1614, 1256, 1174, 1046, 840. MS (ES⁺) m/e 412, Mp (°C)=116-118.

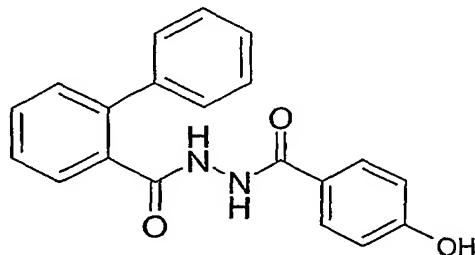
Example 216

Preparation of {3-[4-(5-Biphenyl-2-yl-[1,3,4]oxadiazol-2-yl)phenoxy]propyl}dimethylamine.

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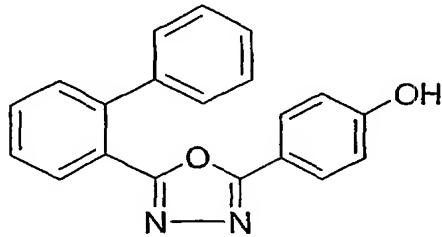
- a) 4-Hydroxybenzoic acid *N'*-(biphenyl-2-caronyl)hydrazide



The above compound was prepared in a manner similar to that exemplified for the
 5 preparation of Example 19c, from 2-biphenylcarboxylic acid (2.42 g, 12.2 mmol), 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (3.02 g, 12.2 mmol) and 4-hydroxybenzoic hydrazide (1.86 g, 12.2 mmol). Purification by chromatography on silica gel (eluted with a linear gradient of 2 to 10% 2M NH₃ in MeOH:CHCl₃) afforded 0.730 g (18%) of 4-hydroxybenzoic acid *N'*-(biphenyl-2-caronyl)hydrazide as a solid.

¹H NMR (DMSO-d6) δ 10.26 (bs, 1H), 10.20 (bs, 1H), 10.08 (bs, 1H), 7.78 (d, 2H, J=8 Hz), 7.30-7.62 (m, 9H), 6.81 (d, 2H, J=9Hz). MS (ES⁺) m/e 333, MS (ES⁻) m/e 331.

- 15 b) 4-(5-biphenyl-2-yl)[1,3,4]oxadiazol-2-ylphenol



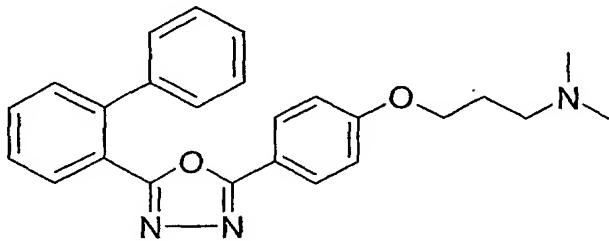
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19d, from 4-hydroxybenzoic acid *N'*-(biphenyl-2-caronyl)hydrazide (0.72 g, 2.2 mmol), triphenylphosphine (1.14 g, 4.3 mmol),

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triethylamine (0.44 g, 4.3 mmol) and carbon tetrabromide (1.44 g, 4.3 mmol). Purification by radial chromatography on silica gel (eluted with 4:1 EtOAc:hexane) afforded the crude product plus an impurity. The material was triturated in Et₂O then filtered. The insoluble material was collected to afford 0.288 g (42%) of 4-(5-biphenyl-2-yl[1,3,4]oxadiazol-2-yl)phenol.

¹H NMR (DMSO-d6) δ10.34 (bs, 1H), 8.05 (d, 1H, J=8Hz), 7.69-7.74 (m, 1H), 7.59-7.65 (m, 1H), 7.52-7.55 (m, 1H), 7.39-7.44 (m, 5H), 7.28-7.33 (m, 2H), 6.83 (d, 2H, J=9 Hz). MS (ES⁺) m/e 315, MS (ES⁻) m/e 313

c) {3-[4-(5-Biphenyl-2-yl-[1,3,4]oxadiazol-2-yl)phenoxy]propyl}dimethylamine

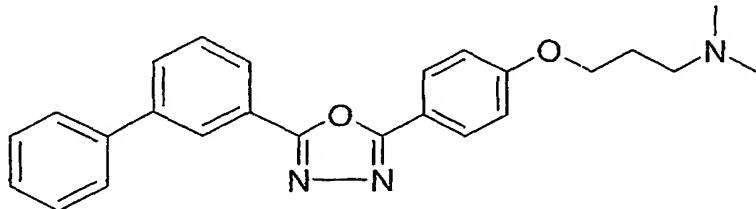


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19e, from 4-(5-biphenyl-2-yl[1,3,4]oxadiazol-2-yl)phenol (0.233 g, 0.7 mmol), sodium hydride (0.065g, 1.6 mmol) and 3-chloro-N,N-dimethylpropyl amine HCl (0.129 g, 8.2 mmol). Purification by radial chromatography on silica gel (eluted with 9:1 CHCl₃: 2M NH₃ in MeOH) followed by conversion to the HCl salt, as described in Example 5 using the acetyl chloride/EtOH method to generate HCl *in situ*. Crystallization from MeOH:Et₂O afforded 0.058 g (18%) of {3-[4-(5-Biphenyl-2-yl-[1,3,4]oxadiazol-2-yl)phenoxy]propyl}dimethylamine as the hydrochloride salt.

¹H NMR (DMSO-d6) δ10.21 (bs, 1H), 8.06-8.09 (m, 1H), 7.70-7.75 (m, 1H), 7.60-7.66 (m, 1H), 7.51-7.57 (m, 3H), 7.40-7.44 (m, 3H), 7.29-7.33 (m, 2H), 7.05 (d, 2H, J=9 Hz), 4.13 (t, 2H, J=6Hz), 3.19 (t, 2H, 8Hz), 2.76 (s, 6H), 2.09-2.17 (m, 2H). IR (KBr, cm⁻¹) 1612, 1498, 1477, 1254, 1178, 1045, 836, 744. MS (ES⁺) m/e 400. Analytical HPLC:100%. Mp=(°C)=177.

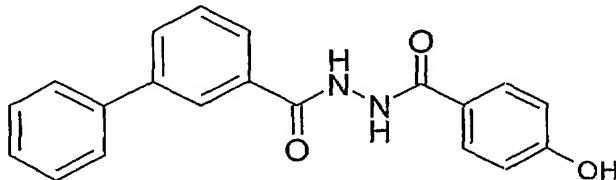
Example 217

Preparation of {3-[4-(5-Biphenyl-3-yl-[1,3,4]oxadiazol-2-yl)phenoxy] propyl} dimethylamine



5

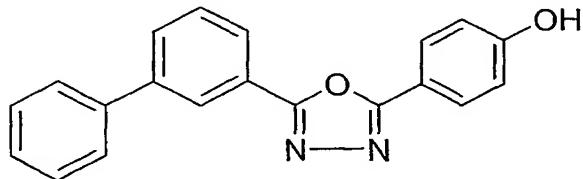
- a) 4-Hydroxybenzoic acid *N'*-(biphenyl-3-caronyl)hydrazide



To a suspension of biphenyl-3-carboxylic acid (1.00 g, 5.0 mmol) in 25 ml CH₂Cl₂ at room temperature was added oxalyl chloride (1.92 g, 15.1 mmol) followed by three drops of DMF. The reaction was stirred at room temperature for 1.8 hours then heated at 40C for four hours. The reaction was then concentrated to an oil. This material was taken up into 41 ml CH₃CN treated with triethylamine (0.510 g, 5.0 mmol), 4-hydroxybenzoic hydrazide (0.786 g, 5.0 mmol) and dimethylamine pyridine (0.062 g, 0.5 mmol). The reaction mixture was heated at 60C for two days then overnight at room temperature. The suspension was concentrated to a solid. The solid was treated with EtOAc and 5N HCl. The resultant suspension was filtered. The phases from the filtrate were separated. The organic phase was washed with 5N HCl, brine, dried over Na₂SO₄, filtered, concentrated to a semi-solid material. Trituration in CHCl₃ followed by filtration afforded the title compound along with an impurity. This material was taken on to the next step.

MS (ES⁺) m/e 333, MS (ES⁻) m/e 331.

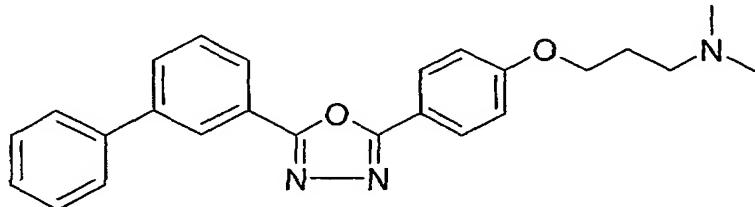
- b) 4-(5-biphenyl-3-yl[1,3,4]oxadiazol-2-yl)phenol



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19d, from of 4-Hydroxybenzoic acid *N'*-(biphenyl-3-caronyl)hydrazide (0.604 g, 1.8 mmol), triphenylphosphine (0.953 g, 3.6 mmol), triethylamine (0.368 g, 3.6 mmol) and carbon tetrabromide (1.205 g, 3.6 mmol).
5 Purification by radial chromatography on silica gel (eluted with EtOAc) afforded 0.379 g (66%) of 4-(5-biphenyl-3-yl)[1,3,4]oxadiazol-2-yl)phenol.

10 ^1H NMR (DMSO-d6) δ 10.34 (s, 1H), 8.33 (s, 1H), 8.10 (d, 1H, J=8Hz), 8.01 (d, 2H, J=8Hz), 7.93 (d, 1H, J=8Hz), 7.69-7.80 (m, 3H), 7.43-7.56 (m, 3H), 6.98 (d, 2H, J=9 Hz). IR (KBr, cm⁻¹) 1735, 1612, 1594, 1495, 1439, 1283, 1240, 1203, 1169, 742, 719, 695. MS (ES⁺) m/e 315, MS (ES⁻) m/e 313.

c) {3-[4-(5-Biphenyl-2-yl-[1,3,4]oxadiazol-3-yl)phenoxy]propyl}dimethylamine



15 The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19e, from 4-(5-biphenyl-3-yl)[1,3,4]oxadiazol-2-yl)phenol (0.0.362 g, 1.2 mmol), sodium hydride (0.101g, 2.5 mmol) and 3-chloro-N,N-dimethylpropyl amine HCl (0.200 g, 1.3 mmol). Purification by radial chromatography on silica gel (eluted with 9:1 CHCl₃: 2M NH₃ in MeOH) followed by crystallization from
20 MeOH:Et₂O afforded 0.083 g (18%) of {3-[4-(5-Biphenyl-2-yl-[1,3,4]oxadiazol-3-yl)phenoxy]propyl}dimethylamine.

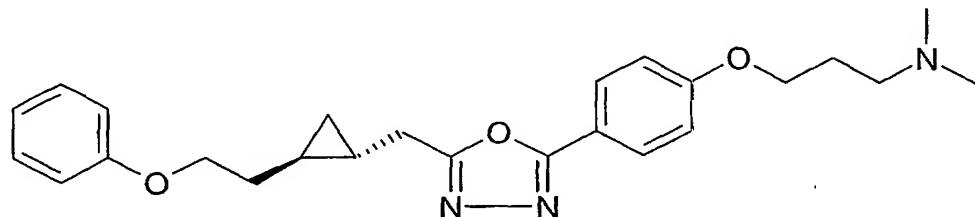
^1H NMR (DMSO-d6) δ 8.35 (s, 1H), 8.09-8.13 (m, 3H), 7.93 (d, 1H, J=8Hz), 7.79 (d, 2H, J=8Hz), 7.72 (t, 1H, J=8Hz), 7.52-7.57 (m, 2H), 7.43-7.48 (m, 1H), 7.16 (d, 2H, J=9Hz), 4.12(t, 2H, J=6Hz), 2.38 (t, 2H, J=7Hz), 2.14 (s, 6H), 1.84-1.93 (m, 2H). IR

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(KBr, cm^{-1}) 2755, 1611, 1497, 1257, 1176, 830, 739, 716. MS (ES^+) m/e 400. Analytical HPLC:100%. Mp($^\circ\text{C}$)=111.

Example 218

- 5 Preparation of Dimethyl-[3-(4-{5-[2-(2-phenoxyethyl)cyclopropylmethyl]-[1,3,4]-oxadiazol-2-yl}phenoxy)propyl]amine

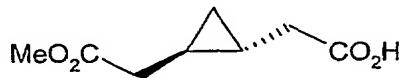


- a) trans-(2-Methoxycarbonylmethylcyclopropyl) acetic acid methyl ester.



- 10 To a suspension of zinc-copper couple (44.82 g (0.35 mol) in 32 ml Et_2O undergoing sonication was added a solution of trans-3-hexene-1,6-dioic acid methyl ester (29.93 g, 0.17 mol) and methyl iodide (65.18 g (0.24 mol) at a rate of 0.5 ml per ten minutes for the 90 minutes then 1.0 ml per ten minutes for the next 1.5 hours of the addition. At this point the addition was stopped and sonication continued for 1.5 hours.
- 15 After this the remaining material was added at a rate of 2.0 ml per ten minutes for the remainder of the addition. The reaction was sonicated overnight. The reaction mixture solidified overnight. The mixture was treated with 800 ml EtOAc then heated to 60 $^\circ\text{C}$ to breakup the solid material. This mixture was treated with filter agent then filtered. The filtrate was concentrated to an oil. The oil was dissolved into Et_2O then washed with 100 ml 10% aqueous HCl , brine, dried over Na_2SO_4 , filtered concentrated to an oil.
- 20 Distillation at 115-120 $^\circ\text{C}$ afforded 9.95 g of a 1:1 mixture of trans-3-hexene-1,6-dioic acid methyl ester and trans-(2-Methoxycarbonylmethylcyclopropyl) acetic acid methyl ester.

- b) trans-(2-Methoxycarbonylmethylcyclopropyl) acetic acid



25

To a biphasic solution of trans-(2-methoxycarbonylmethylcyclopropyl) acetic acid methyl ester (10.95 g, 58.8 mmol) in 200 ml aqueous potassium phosphate mono basic (2.76 g) was added porcine liver esterase (123 mg, approximately 5,060 units). Next, 58.8 ml 1N LiOH solution was added in portions, maintaining pH between 7.0 and 7.5, over a 5 two-hour period. The reaction was stirred overnight at room temperature. Next, filter aid was added and the reaction was filtered. The filtrate was extracted twice with Et₂O and the organic layer was discarded. The aqueous phase was acidified with 1N HCl then extracted twice with Et₂O. The combined organic phases were dried over Na₂SO₄, filtered, concentrated to afford 6.65 g of a 3:2 ratio of trans-hex-3-enedioic acid 10 monomethyl ester : trans-(2-methoxycarbonylmethylcyclopropyl) acetic acid.

¹H NMR of title compound (DMSO-d₆) δ3.57 (s, 3H), 2.01-2.33 (m, 4H), 0.76-0.82 (m, 2H), 0.32-0.38 (m, 2H). MS (ES⁻) m/e 171.

c) trans-[2-(2-hydroxyethyl)cyclopropyl]acetic acid methyl ester



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 22a, from 3:2 ratio of trans-hex-3-enedioic acid monomethyl ester : trans-(2-methoxycarbonylmethylcyclopropyl) acetic acid (8.49 g) to afford 1.47 g mixture of 6-hydroxy-trans-hex-3-enoic acid methyl ester and trans-[2-(2-hydroxyethyl)cyclopropyl]acetic acid methyl ester.

d) trans-[2-(2-phenoxyethyl)cyclopropyl]acetic acid methyl ester



To a mixture of trans-6-hydroxy-hex-3-enoic acid methyl ester and trans-[2-(2-hydroxyethyl)cyclopropyl]acetic acid methyl ester (1.47 g), phenol (0.962 g, 10.2 mmol) and triphenylphosphine (2.68g, 10.2 mmol) in 28 ml THF at 0C was added dropwise diisopropylazodicarboxylate (2.07 g, 10.2 mmol). The reaction was stirred overnight at room temperature. The mixture was concentrated to an oil. The oil was diluted with 50 ml EtOAc then washed twice with 1N NaOH, once with brine, dried over Na₂SO₄, filtered, 25 concentrated to an oil. Purification by chromatography on silica gel (eluted with 30 25% EtOAc/hexanes).

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EtOAc:hexane) followed by a second purification using chromasil (eluted with linear gradient of 30 to 60% CH₂Cl₂:hexane) afforded a 3:2 ratio of trans-[2-(2-phenoxyethyl)cyclopropyl]acetic acid methyl ester and 6-phenoxy-trans-hex-3-enoic acid methyl ester.

5 The mixture of trans-[2-(2-phenoxyethyl)cyclopropyl]acetic acid methyl ester and 6-phenoxy-trans-hex-3-enoic acid methyl ester (0.954 g) in 3 ml MeOH at -78C was treated with ozone until a blue haze persisted in the reaction mixture. Nitrogen was then bubbled through the reaction mixture. Next, dimethyl sulfide (0.354 g, 5.7 mmol) was added and stirring continued until the cooling bath warmed to room temperature, 10 approximately 2.5 hours. The solution was then concentrated to an oil.

The oil was dissolved into 25 ml acetone then Jones Reagent (2.5 ml, 8.2 mmol) was added. After stirring at room temperature for five minutes the reaction was quenched with aqueous sodium thiosulfate was added. The product was extracted with Et₂O (2 x 50 ml), organic phases combined, washed with saturated aqueous sodium bicarbonate (2 x 50 ml), brine, dried over Na₂SO₄, filtered, concentrated to an oil. Purification by radial chromatography on silica gel (eluted with 3:1 hexane:Et₂O) afforded 0.395 g of trans-[2-(2-phenoxyethyl)cyclopropyl]acetic acid methyl ester as an oil. 15

15 ¹H NMR (DMSO-d6) δ 7.24-7.30 (m, 2H), 6.88-6.93 (m, 3H), 3.99 (t, 2H, J=7 Hz), 3.52 (s, 3H), 2.15-2.35 (m, 2H), 1.54-1.73 (m, 2H), 0.66-0.84 (m, 2H), 0.31-0.41 (m, 2H). MS (TOF) m/e 170.

e) trans-[2-(2-phenoxyethyl)cyclopropyl]acetic acid



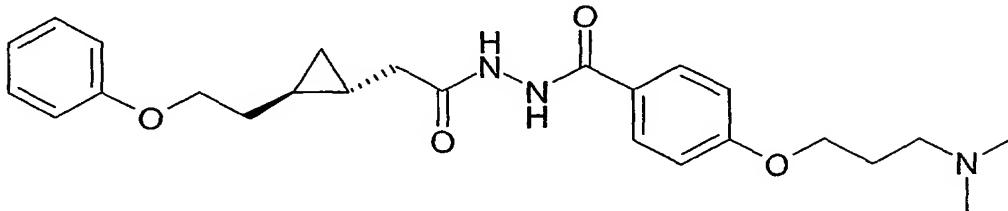
20 The above compound was prepared in a manner similar to that exemplified for the preparation of Example 1a, from trans[2-(2-phenoxyethyl) cyclopropyl] acetic acid methyl ester (0.371 g, 1.6 mmol) and lithium hydroxide (0.114 g, 4.8 mmol) afforded 0.291 g of trans-[2-(2-phenoxyethyl)cyclopropyl]acetic acid as an oil that crystallizes out.

25 ¹H NMR (DMSO-d6) δ 7.24-7.30 (m, 2H), 6.88-6.95 (m, 3H), 4.01(t, 2H, J=7 Hz), 2.06-2.24 (m, 2H), 1.59-1.68 (m, 2H), 0.75-0.84 (m, 1H), 0.63-0.71 (m, 1H), 0.29-0.39 (m, 2H). IR (KBr, cm⁻¹) 3038, 2999, 2947, 2928, 1713, 1601, 1499, 1254, 1244,

-411-

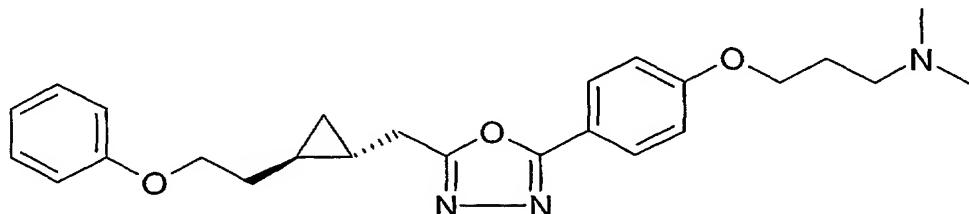
1225, 1210, 1038, 754, 692. MS (ES⁻) m/e 219. Anal. Calcd for C₁₃H₁₆O₃ C, 70.89; H, 7.32. Found C, 70.75; H, 7.50.

- f) 4-(3-Dimethylaminopropoxy)benzoic acid N'-trans-{2-[2-(2-phenoxyethyl)cyclopropyl] acetyl}hydrazide



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19c, from of trans-[2-(2-phenoxyethyl)cyclopropyl]acetic acid (0.274 g, 1.2 mmol), 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (0.308 g, 1.2 mmol) and 4-hydroxybenzoic hydrazide (0.295 g, 1.2 mmol). Purification by radial chromatography on silica gel (eluted with 95:5 CHCl₃:2M NH₃ in MeOH:CHCl₃). afforded 0.055 g (10%) of 4-(3-dimethylaminopropoxy)benzoic acid N'-trans-{2-[2-(2-phenoxyethyl)cyclopropyl] acetyl}hydrazide.

- g) Dimethyl-[3-(4-{5-[2-(2-phenoxyethyl)cyclopropylmethyl]-[1,3,4]-oxadiazol-2-yl}phenoxy)propyl]amine



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 19d, from 4-(3-dimethylaminopropoxy)benzoic acid N'-trans-{2-[2-(2-phenoxyethyl)cyclopropyl] acetyl}hydrazide (0.055 g, 0.13 mmol), triphenylphosphine (0.066 g, 0.25 mmol), triethylamine (0.025 g, 0.25 mmol) and carbon tetrabromide (0.083 g, 0.25 mmol). Purification by radial chromatography on silica gel (eluted with 9:1 CHCl₃:2M NH₃ in MeOH) followed by formation of the oxalate salt

-412-

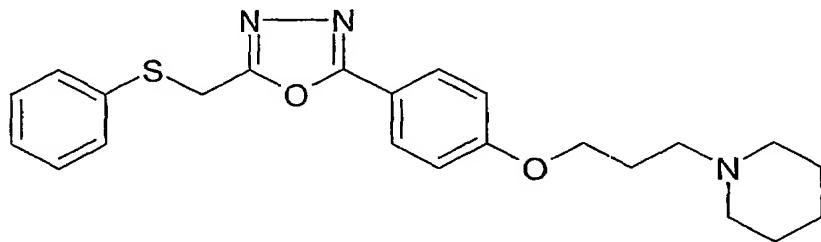
afforded 0.061 (95%) g of dimethyl-trans-[3-(4-{5-[2-(2-phenoxyethyl)cyclo propyl methyl]-[1,3,4]-oxadiazol-2-yl}phenoxy)propyl]amine as the oxalate salt.

¹H NMR (DMSO-d₆) δ 7.90 (d, 2H, J=9Hz), 7.18-7.23 (m, 2H), 7.10 (d, 2H, J=9Hz), 6.81-6.90 (m, 3H), 4.13(t, 2H, J=6Hz), 3.94-3.99 (m, 2H), 3.13-3.18 (m, 2H), 2.94-5 3.01 (m, 1H), 2.73-2.81 (m, 7H), 2.09-2.14 (m, 2H), 1.73-1.79 (m, 1H), 1.51-1.61 (m, 1H), 0.96-1.02 (m, 1H), 0.83—0.93 (m, 1H), 0.45-0.57 (m, 2H). IR (KBr, cm⁻¹) 3042, 2937, 2869, 1720, 1615, 1501, 1472, 1257, 1176, 476. MS (ES⁺) m/e 421. Anal. Calcd for C₂₅H₃₁N₃O₃ C₂H₂O₄ C, 63.39; H, 6.50; N, 8.21. Found C, 63.35; H, 6.55; N, 8.22. Mp(°C)=141.

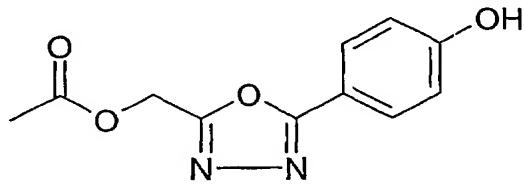
10

Example 219

Preparation of 1-{3-[4-(5-Phenylsulfanyl methyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl piperidine



15 a) Acetic acid 5-(4-hydroxyphenyl)-[1,3,4]oxadiazol-2-ylmethyl ester

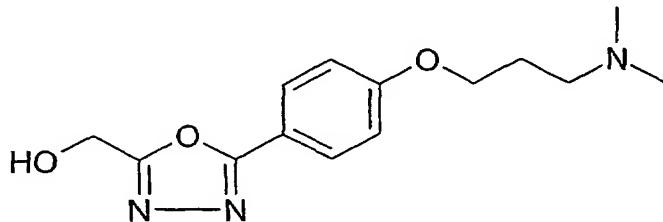


To 4-hydroxybenzoic hydrazide (4.39 g, 28.9 mmole) in 145 ml CH₃CN and 35 ml THF at room temperature was added a solution of acetoxyacetyl chloride (3.59 g, 26.3 mmol) in 30 ml CH₃CN over a five-minute period. The suspension was then stirred at 20 room temperature for two hours. To this suspension was added triethylamine (6.38 g, 63.0 mmol), triphenylphosphine (8.26 g, 31.5 mmol) and carbon tetrabromide (10.45 g, 31.5 mmol). The resultant red solution was stirred 16 hours at room temperature. The mixture was concentrated to an oil. The oil was diluted with 250 ml EtOAc then washed with 0.1 N HCl (2 x 250ml), brine (250ml), dried over Na₂SO₄, filtered, concentrated to 25 afford a red oil. Purification from chromatography on silica gel (eluted with EtOAc)

afforded a solid. Crystallization from Et₂O afforded 1.99 g of the title compound. The filtrate from the crystallization was concentrated to afford an additional 1.06 g of the title compound. A total of 3.05 g (50%) of acetic acid 5-(4-hydroxyphenyl)-[1,3,4]oxadiazol-2-ylmethyl ester was isolated.

5 ¹H NMR (DMSO-d6) δ 10.33 (bs, 1H), 7.81 (d, 2H, J=9Hz), 6.93 (d, 2H, J=9 Hz), 5.33 (s, 2H), 2.12 (s, 3H). IR (KBr, cm⁻¹) 3147, 1757, 1606, 1590, 1512, 1443, 1411, 1369, 1285, 1211, 1181, 1094, 1066, 968, 846, 741, 626, 521. MS (ES⁺) m/e 235, MS (ES⁻) m/e 233.

10 b) 5-[4-(3-Piperidin-1-yl-propoxy)phenyl]-[1,3,4]oxadiazol-2-yl}methanol

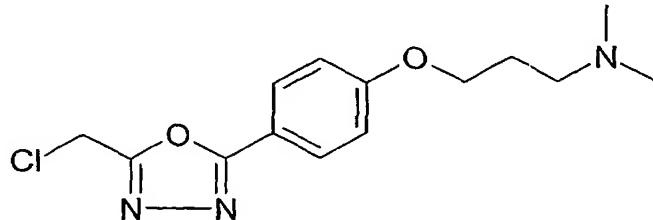


To acetic acid 5-(4-hydroxyphenyl)-[1,3,4]oxadiazol-2-ylmethyl ester (4.96 g, 21.2 mmol), triphenyl phosphine (8.33 g, 31.8 mmol) and 3-N-piperidino-1-propanol (4.79 g, 31.8 mmol) in 65 ml THF at 0C was added diisopropylazodicarboxylate 6.42 g, 31.8 mmol) over a ten minute period. The resultant orange solution was stirred at room temperature for six hours. Next, 50ml 1N NaOH was added and the reaction was stirred thirty minutes at room temperature. The reaction mixture was then extracted with EtOAc (2 x 100 ml). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated to an oil. Purification by chromatography on silica gel (eluted 15 with a step gradient of 5L CH₂Cl₂, 5L 5% 2M NH₃ IN MeOH:CH₂Cl₂, 5L 7.5% 2M NH₃ IN MeOH:CH₂Cl₂) to afford an oil. Treatment of the oil with Et₂O resulted in a suspension. The insoluble material was collected by filtration to afford 4.64 g (69%) of {5-[4-(3-piperidin-1-yl-propoxy)phenyl]-[1,3,4]oxadiazol-2-yl}methanol.

20 ¹H NMR (DMSO-d6) δ 7.89 (d, 2H, J=9Hz), 7.10 (d, 2H, J=9Hz), 5.91 (t, 1H, J=6Hz), 4.67 (d, 2H, J=6Hz), 4.09 (t, 2H, J=6Hz), 2.25-2.42 (m, 6H), 1.85-1.93 (m, 2H), 1.44-1.54 (m, 4H), 1.32-1.41 (m, 2H). IR (KBr, cm⁻¹) 3061, 2935, 2811, 1618, 1499, 1464, 1430, 1311, 1260, 1176, 1126, 1053, 839, 780, 738, 679, 528. MS (ES⁺) m/e 318.

-414-

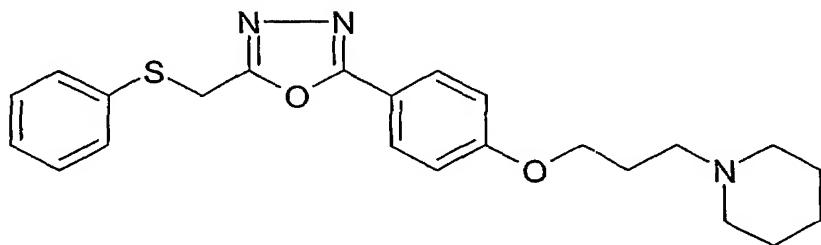
c) 1-{3-[4-(5-Chloromethyl-[1,3,4]oxadiazol-2-yl)phenoxy]propyl}piperidine



To {5-[4-(3-piperidin-1-yl-propoxy)phenyl]-[1,3,4]oxadiazol-2-yl}methanol (0.159 g, 0.5mmol) in 5.0 ml CH₂Cl₂ at room temperature was added thionyl chloride (1.67 g, 14.03mmol). The reaction was stirred at room temperature for 1.5 hours then concentrated to a solid. This material was dissolved into CH₂Cl₂:H₂O and 1N NaOH added until pH was greater than 12. The phases were separated, aqueous phase extracted with CH₂Cl₂. The organic phases were combined, washed with brine, dried over Na₂SO₄, filtered, concentrated to afford 0.146 g (87%) of 1-{3-[4-(5-chloromethyl-[1,3,4]oxadiazol-2-yl)phenoxy]propyl}piperidine as a crystalline solid.

¹H NMR (DMSO-d6) δ 7.90 (d, 2H), 7.13 (d, 2H), 5.09 (s, 2H), 3.08 (t, 2H), 2.26-2.40 (m, 6H), 1.84-1.93 (m, 2H), 1.45-1.51 (m, 4H), 1.33-1.40 (m, 2H). MS (ES⁺) m/e 336.

15 d) 1-{3-[4-(5-Phenylsulfanylmethyl-[1,3,4]oxadiazol-2-yl)phenoxy]propyl}piperidine



Method A: A suspension of 1-{3-[4-(5-chloromethyl-[1,3,4]oxadiazol-2-yl)phenoxy]propyl}piperidine (0.071 g, 0.21mmol) , cesium carbonate (0.076 g, 0.23 mmol) and benzenethiol (0.026 g, 0.23 mmol)in 1.0 ml acetone was stirred at room temperature for 1.0 hour refluxed for 1.0 hour. After cooling to room temperature the suspension was filtered.

Method B: To benzenethiol (0.026 g, 0.23 mmol) in 1.0 ml THF was added sodium hydride (0.009 g, 0.23 mmol) at room temperature. The mixture was stirred five

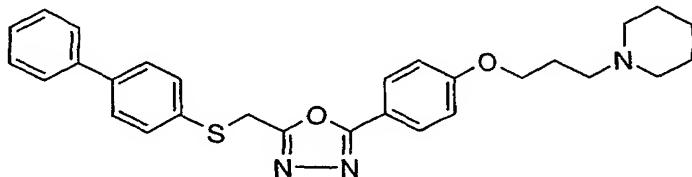
minutes then 1-{3-[4-(5-chloromethyl-[1,3,4]oxadiazol-2-yl)phenoxy]propyl}piperidine (0.071 g, 0.23 mmol) was added. The reaction mixture was stirred at room temperature for 1.0 hour then refluxed for 1.0 hour. After cooling to room temperature the suspension was filtered.

5 The filtrates from Method A and Method B were combined, concentrated in vacuo. Purification by radial chromatography (eluted with 5% 2M NH₃ in MeOH:CH₂Cl₂) followed by conversion to the HCl salt, as described in Example 5 using the acetyl chloride/EtOH method to generate HCl *in situ*, afforded 0.066 g (35%) of 1-{3-[4-(5-Phenylsulfanyl methyl-[1,3,4]oxadiazol-2-yl)phenoxy]propyl}piperidine as the
10 hydrochloride salt.

¹H NMR (DMSO-d6) δ 10.10 (bs, 1H), 7.81 (d, 2H, J=9Hz), 7.44-7.47 (m, 2H), 7.32-7.37 (m, 2H), 7.24-7.28 (m, 1H), 7.12 (d, 2H, J=9Hz), 4.57 (s, 2H), 4.20 (t, 2H, J=6 Hz), 3.43-3.46 (m, 2H), 3.13-3.20 (m, 2H), 2.81-2.92 (m, 2H), 2.16-2.25 (m, 2H), 1.66-1.82 (m, 5H), 1.33-1.42 (m, 1H). IR (KBr, cm⁻¹) 2940, 2621, 2503, 1615, 1499, 1440, 15 1393, 1309, 1250, 1178, 1054, 1015, 976, 943, 840, 742, 688. MS (ES⁺) m/e 410. Anal. Calcd for C₂₃H₂₇N₃O₂S HCl C, 61.94; H, 6.33; N, 9.42. Found C, 61.62; H, 6.38; N, 9.28. Analytical HPLC: 100%. Mp(°C)=152.

Example 220

20 Preparation of 1-(3-{4-[5-(biphenyl-4-ylsulfanyl methyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)piperidine



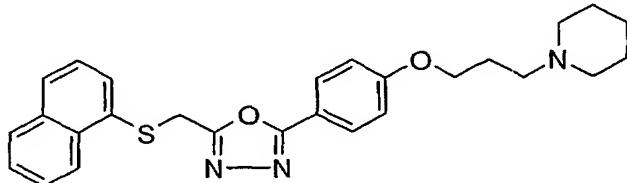
To a solution of biphenyl-4-thiol (0.153 g, 0.82 mmol) in 3.5 ml THF at room temperature was added sodium hydride (0.033 g, 0.82 mmol). The reaction mixture was 25 stirred five minutes then 1-{3-[4-(5-chloromethyl-[1,3,4]oxadiazol-2-yl)phenoxy]propyl}piperidine (0.250 g, 0.74 mmol) was added followed by 2ml THF. The reaction was heated at 60C for one hour. After cooling to room temperature the reaction was diluted with 50 ml H₂O and extracted with EtOAc (2 x 50 ml). The organic phases were washed with brine, dried over Na₂SO₄, filtered, concentrated *in vacuo*. Purification by

radial chromatography (eluted with 5% 2M NH₃ in MeOH:CH₂Cl₂) followed by conversion to the HCl salt, as described in Example 5 using the acetyl chloride/EtOH method to generate HCl *in situ*, afforded 0.088 g (23%) of 1-(3-{4-[5-(biphenyl-4-ylsulfanyl)methyl]-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)piperidine as the hydrochloride salt.

¹H NMR (DMSO-d6) δ 107.84 (d, 2H, J=9Hz), 7.66 (d, 4H, J=8Hz), 7.55 (d, 2H, J=8Hz), 7.44-7.49 (m, 2H), 7.35-7.39 (m, 1H), 7.10 (d, 2H, J=9Hz), 4.63 (s, 2H), 4.14 (t, 2H, J=6Hz), 3.39-3.50 (m, 2H), 3.11-3.22 (m, 2H), 2.81-2.92 (m, 2H), 2.11-2.22 (m, 2H), 1.61-1.85 (m, 5H), 1.31-1.42 (m, 1H). IR (KBr, cm⁻¹) 3420, 3053, 3027, 2940, 2612, 2488, 1615, 1500, 1479, 1300, 1254, 1174, 1085, 1005, 948, 835, 761, 698. MS (ES⁺) m/e 486. Mp(°C)=142.

Example 221

Preparation of 1-(3-{4-[5-(Naphthalen-1-ylsulfanyl)methyl]-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)piperidine



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 220 from 1-naphthalenethiol (0.131 g, 0.82 mmol), 1-{3-[4-(5-chloromethyl-[1,3,4]oxadiazol-2-yl)phenoxy] propyl}piperidine (0.250 g, 0.74 mmol) and sodium hydride (0.033g, 0.82 mmol) to afford 0.162 g (44%) of 1-(3-{4-[5-(naphthalen-1-yl-sulfanyl)methyl]-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)piperidine as the hydrochloride salt.

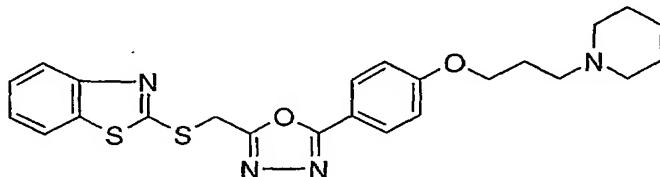
¹H NMR (DMSO-d6) δ 8.24-8.29 (m, 1H), 7.91-8.00 (m, 2H), 7.79 (d, 1H, J=7 Hz), 7.70 (d, 2H, J=9Hz), 7.48-7.58 (m, 3H), 7.08 (d, 2H, J=9Hz), 4.58 (s, 2H), 4.15 (t, 2H, J=6Hz), 3.37-3.45 (m, 2H), 3.13-3.22 (m, 2H), 3.81-3.94 (m, 2H), 2.11-2.34 (m, 2H), 1.65-1.84 (m, 5H), 1.31-1.43 (m, 1H). IR (KBr, cm⁻¹) 3050, 2947, 2462, 2403, 1615, 1591, 1497, 1465, 1427, 1307, 1252, 1171, 1066, 950, 844, 793, 767. MS (ES⁺) m/e

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460. Anal. Calcd for C₂₇H₂₉N₃O₂S HCl C, 65.37; H, 6.10; N, 8.47. Found C, 65.13; H, 6.09; N, 8.22. Mp(°C)=195.

Example 222

- 5 Preparation of 2-{5-[4-(3-Piperidin-1-yl-propoxy)phenyl]-[1,3,4]oxadiazol-2-ylmethylsulfanyl}benzothiazole



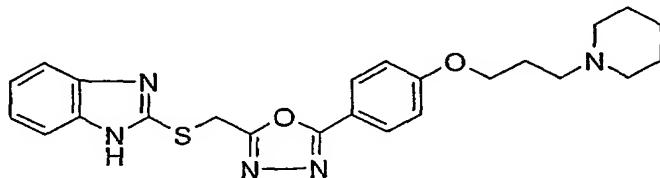
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 220 from 2-mercaptopbenzothiazole (0.137 g, 0.82 mmol), 1-{3-[4-(5-chloromethyl-[1,3,4]oxadiazol-2-yl)phenoxy] propyl}piperidine (0.250 g, 0.74 mmol) and sodium hydride (0.033g, 0.82 mmol) to afford 0.170 g (49%) of 2-{5-[4-(3-piperidin-1-yl-propoxy)phenyl]-[1,3,4]oxadiazol-2-ylmethylsulfanyl}benzothiazole as the hydrochloride salt.

10 ¹H NMR (DMSO-d₆) δ 8.05 (d, 1H, J=8Hz), 7.85-7.90 (m, 3H), 7.45-7.51 (m, 1H), 7.38-7.44 (m, 1H), 7.12 (d, 2H, J=7Hz), 5.01 (s, 2H), 4.15 (t, 2H, J=6Hz), 3.39-3.50 (m, 2H), 3.13-3.22 (m, 2H), 2.81-2.93 (m, 2H), 2.12-2.23 (m, 2H), 1.64-1.84 (m, 5H), 1.31-1.41 (m, 1H). IR (KBr, cm⁻¹) 3431, 2948, 2617, 2486, 1612, 1499, 1457, 1426, 1306, 1253, 1175, 1049, 1004, 942, 835, 753, 724. MS (ES⁺) m/e 467. Mp(°C)=144.

20

Example 223

- Preparation of 2-{5-[4-(3-piperidin-1-yl-propoxy)phenyl]-[1,3,4]oxadiazol-2-ylmethylsulfanyl}-1*H*-benzimidazole



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 220 from 2-mercaptopbenzimidazole (0.246 g, 1.64 mmol), 1-{3-[4-(5-chloromethyl-[1,3,4]oxadiazol-2-yl)phenoxy] propyl}piperidine (0.500 g, 1.49

-418-

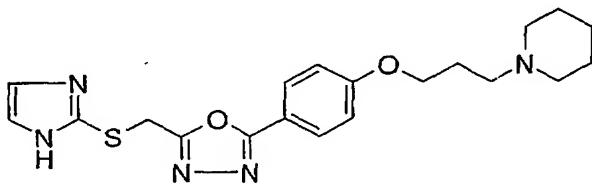
mmol) and sodium hydride (0.066 g, 1.64 mmol) to afford 0.364 g (54%) of 2-{5-[4-(3-piperidin-1-yl-propoxy)phenyl]-[1,3,4]oxadiazol-2-ylmethylsulfanyl}-1*H*-benzimidazole.

¹H NMR (DMSO-d₆) δ 7.75 (d, 2H), 7.33-7.54 (m, 2H), 7.10-7.15 (m, 2H), 7.04 (d, 2H), 4.85 (s, 2H), 4.05 (t, 2H), 2.26-2.39 (m, 6H), 1.83-1.91 (m, 2H), 1.45-1.50 (m, 4H), 1.33-1.40 (m, 2H). IR (KBr, cm⁻¹) 3068, 2935, 2878, 2803, 1619, 1500, 1430, 1401, 1352, 1301, 1252, 1179, 1008, 841, 741, 523. MS (ES⁺) m/e 450. Anal. Calcd for C₂₄H₂₇N₅O₂S C, 64.12; H, 6.05; N, 15.58. Found C, 64.07; H, 6.06; N, 15.41. Mp(°C)=193.

10

Example 224

Preparation of 1-(3-{4-[5-(1*H*-Imidazol-2-ylsulfanyl)methyl]-[1,3,4]oxadiazol-2-yl}phenoxy}propyl)piperidine



15

The above compound was prepared in a manner similar to that exemplified for the

preparation of Example 220 from 2-mercaptopimidazole (0.082 g, 0.82 mmol), 1-{3-[4-(5-chloromethyl-[1,3,4]oxadiazol-2-yl)phenoxy] propyl}piperidine (0.250 g, 0.74 mmol) and sodium hydride (0.033g, 0.82 mmol) to afford 0.128 g (43%) of 1-(3-{4-[5-(1*H*-imidazol-2-ylsulfanyl)methyl]-[1,3,4]oxadiazol-2-yl}phenoxy}propyl)piperidine.

20

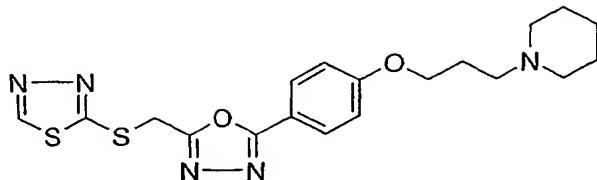
¹H NMR (DMSO-d₆) δ 7.79 (d, 2H, J=9Hz), 7.25 (s, 1H), 7.08 (d, 2H, J=9Hz), 4.40 (s, 2H), 4.05 (t, 2H, J=6Hz), 2.24-2.39 (m, 6H), 1.77-1.92 (m, 2H), 1.39-1.52 (m, 4H), 1.30-1.39 (m, 2H). IR (KBr, cm⁻¹) 2992, 2937, 2765, 1616, 1500, 1428, 1329, 1303, 1250, 1179, 1098, 1007, 960, 846, 756, 657. MS (ES⁺) m/e 400. Anal. Calcd for C₂₀H₂₅N₅O₂S C, 60.13; H, 6.31; N, 17.53. Found C, 59.84; H, 6.19; N, 17.27. Mp(°C)=132.

25

Example 225

Preparation of 1-(3-{4-[5-([1,3,4]thiadiazol-2-ylsulfanyl)methyl]-[1,3,4]oxadiazol-2-yl}phenoxy}propyl)piperidine

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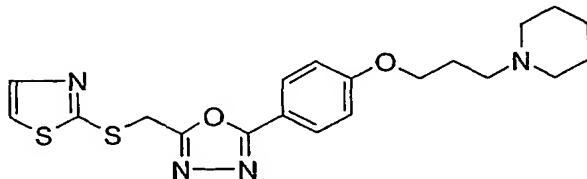
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 220 from 2-mercaptop-1,3,4-thiadiazole (0.097 g, 0.82 mmol), 1-{3-[4-(5-chloromethyl-[1,3,4]oxadiazol-2-yl)phenoxy] propyl}piperidine (0.250 g, 0.74 mmol) and sodium hydride (0.033g, 0.82 mmol) to afford 0.154 g (46%) of 1-(3-{4-[5-([1,3,4]thiadiazol-2-ylsulfanyl)methyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)piperidine220 as the hydrochloride salt.

¹H NMR (DMSO-d6) δ 9.56 (s, 1H), 7.86 (d, 2H, J=9Hz), 7.12 (d, 2H, J=9Hz), 4.92 (s, 2H), 4.15 (t, 2H, J=6Hz), 3.42-3.48 (m, 2H), 3.14-3.20 (m, 2H), 2.81-2.89 (m, 2H), 2.15-2.22 (m, 2H), 1.66-1.82 (m, 5H), 1.33-1.39 (m, 1H).IR (KBr, cm⁻¹) 2945, 2634, 2508, 1615, 1498, 1429, 1367, 1310, 1254, 1175, 1060, 974, 944, 840, 739. MS (ES⁺) m/e 418, MS (ES⁻) m/e 416. Analytical HPLC: 100%. Anal. Calcd for C₁₉H₂₃N₅O₂S₂ HCl C, 50.27; H, 5.33; N, 15.43. Found C, 50.09; H, 5.31; N, 15.17. Mp(°C)=164.

15

Example 226

Preparation of 1-(3-{4-[5-(thiazol-2-ylsulfanyl)methyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)piperidine



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 220 from 2-mercaptopthiazole (0.096 g, 0.82 mmol), 1-{3-[4-(5-chloromethyl-[1,3,4]oxadiazol-2-yl)phenoxy] propyl}piperidine (0.250 g, 0.74 mmol) and sodium hydride (0.033g, 0.82 mmol) to afford 0.154 g (46%) of 1-(3-{4-[5-(thiazol-2-ylsulfanyl)methyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)piperidine as the hydrochloride salt.

¹H NMR (DMSO-d6) δ 7.85 (d, 2H, J=9Hz), 7.78 (s, 1H), 7.74 (s, 1H), 7.12 (d, 2H, J=9Hz), 4.79 (s, 2H), 4.15 (t, 2H, J=6Hz), 3.41-3.46 (m, 2H), 3.13-3.20 (m, 2H),

-420-

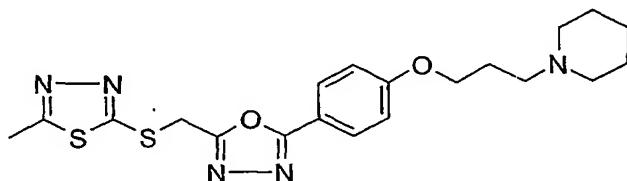
2,82-2.90 (m, 2H), 2.12-2.20 (m, 2H), 1.75-1.81 (m, 2H), 1.63-1.72 (m, 2H), 1.32-1.39 (m, 1H). IR (KBr, cm⁻¹) 3074, 2963, 2940, 2918, 2618, 2499, 1614, 1498, 1472, 1430, 1310, 1251, 1180, 1034, 942, 838, 738, 662. MS (ES⁺) m/e 417, MS (ES⁻) m/e 415.

Analytical HPLC: 100%. Anal. Calcd for C₂₀H₂₄N₄O₂S₂ HCl C, 53.03; H, 5.56; N, 12.37.

5 Found C, 52.92; H, 5.54; N, 12.17. Mp(°C)=174-176.

Example 227

Preparation of 1-(3-{4-[5-(5-methyl-[1,3,4]thiadiazol-2-ylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenoxy} propyl)piperidine



10

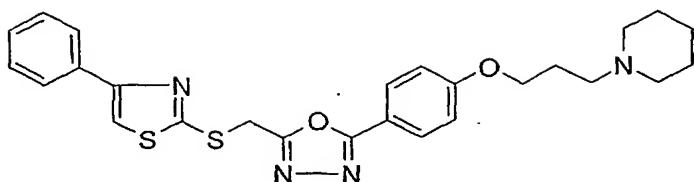
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 220 from 2-mercaptop-5-methyl-1,3,4-thiadiazole (0.108 g, 0.82 mmol), 1-{3-[4-(5-chloromethyl-[1,3,4]oxadiazol-2-yl)phenoxy] propyl}piperidine (0.250 g, 0.74 mmol) and sodium hydride (0.033g, 0.82 mmol) to afford 0.163 g (32%) of 1-(3-{4-[5-(5-methyl-[1,3,4]thiadiazol-2-ylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl) piperidine.

15 ¹H NMR (DMSO-d6) δ 7.83 (d, 2H, J=9Hz), 7.11 (d, 2H, J=9Hz), 4.85 (s, 2H), 4.08 (t, 2H, J=7Hz), 2.69 (s, 3H), 2.25-2.39 (m, 6H), 1.81-1.89 (m, 2H), 1.43-1.51 (m, 4H), 1.32-1.39 (m, 2H). IR (KBr, cm⁻¹) 2933, 2807, 1608, 1499, 1421, 1387, 1307, 1262, 20 1176, 1125, 1068, 1018, 954, 854, 741. MS (ES⁺) m/e 432, MS (ES⁻) m/e 430. Analytical HPLC: 100%. Anal. Calcd for C₂₀H₂₅N₅O₂S₂ C, 55.66; H, 5.84; N, 16.23. Found C, 55.75; H, 5.86; N, 16.08. Mp(°C)=89.

Example 228

25 Preparation of 1-(3-{4-[5-(4-Phenylthiazol-2-ylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)piperidine

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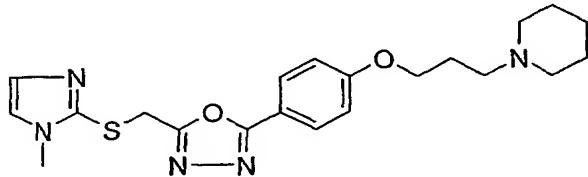


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 220 from 2-mercapto-4-phenylthiazole (0.158 g, 0.82 mmol), 1-{3-[4-(5-chloromethyl-[1,3,4]oxadiazol-2-yl)phenoxy] propyl}piperidine (0.250 g, 0.74 mmol) and sodium hydride (0.033g, 0.82 mmol) to afford 0.080 g (39%) of 1-(3-{4-[5-(4-phenylthiazol-2-ylsulfanyl)methyl]-[1,3,4]oxadiazol-2-yl}phenoxy)propyl)piperidine as the hydrochloride salt.

10 ¹H NMR (DMSO-d6) δ 8.08 (s, 1H), 7.86-7.88 (m, 4H), 7.29-7.39 (m, 3H), 7.10 (d, 2H, J=9Hz), 4.86 (s, 2H), 4.14 (t, 2H, J=6Hz), 3.41-3.47 (m, 2H), 3.13-3.20 (m, 2H), 2.81-2.92 (m, 2H), 2.14-2.22 (m, 2H), 1.65-1.82 (m, 5H), 1.33-1.41 (m, 1H). IR (KBr, cm⁻¹) 2947, 2616, 2468, 2412, 1614, 1498, 1476, 1424, 1306, 1252, 1174, 1034, 839, 729. MS (ES⁺) m/e 493, MS (ES⁻) m/e 491. Analytical HPLC: 100%. Mp(°C)=141.

Example 229

15 Preparation of 1-(3-{4-[5-(1-methyl-1*H*-imidazol-2-ylsulfanyl)methyl]-[1,3,4]oxadiazol-2-yl}phenoxy)propyl)piperidine



20 The above compound was prepared in a manner similar to that exemplified for the preparation of Example 220 from 2-mercapto-1-methylimidazole (0.093 g, 0.82 mmol), 1-{3-[4-(5-chloromethyl-[1,3,4]oxadiazol-2-yl)phenoxy] propyl}piperidine (0.250 g, 0.74 mmol) and sodium hydride (0.033g, 0.82 mmol) to afford 0.228 g (37%) of 1-(3-{4-[5-(1-methyl-1*H*-imidazol-2-ylsulfanyl)methyl]-[1,3,4]oxadiazol-2-yl}phenoxy)propyl)piperidine as the hydrochloride salt.

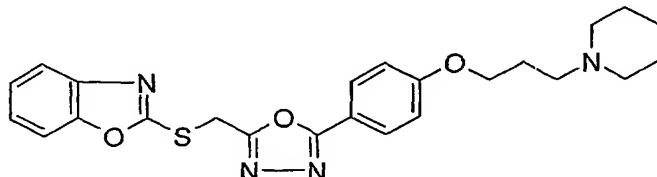
25 ¹H NMR (DMSO-d6) δ 7.84 (d, 2H, J=9Hz), 7.57 (s, 1H), 7.36 (s, 1H), 7.13 (d, 2H, J=9Hz), 4.58 (s, 2H), 4.15 (t, 2H, J=6Hz), 3.67 (s, 3H), 3.40-3.47 (m, 2H), 3.11-3.47 (m, 2H), 2.82-2.92 (m, 2H), 2.14-2.23 (m, 2H), 1.63-1.82 (m, 5H), 1.31-1.42 (m, 1H). IR

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(KBr, cm^{-1}) 3418, 2946, 2615, 2488, 1899, 1615, 1570, 1499, 1471, 1428, 1299, 1251, 1178, 1056, 943, 837, 736. MS (ES^+) m/e 414. Mp($^\circ\text{C}$)=173.

Example 230

- 5 Preparation of 2-{5-[4-(3-Piperidin-1-yl-propoxy)phenyl]-[1,3,4]oxadiazol-2-ylmethylsulfanyl}benzooxazole



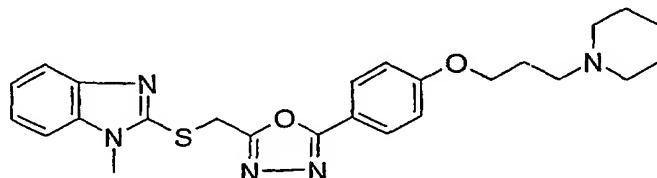
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 220 from 2-mercaptobenzoxazole (0.099 g, 0.66 mmol), 1-{3-[4-(5-chloromethyl-[1,3,4]oxadiazol-2-yl)phenoxy] propyl}piperidine (0.200 g, 0.60 mmol) and sodium hydride (0.026g, 0.66 mmol) to afford 0.097 g (27%) of 2-{5-[4-(3-Piperidin-1-yl-propoxy)phenyl]-[1,3,4]oxadiazol-2-ylmethylsulfanyl}benzooxazole

10 ^1H NMR (DMSO-d6) δ 7.81 (d, 2H, J=9Hz), 7.64-7.68 (m, 2H), 7.32-7.37 (m, 2H), 7.08 (d, 2H, J=9Hz), 4.95 (s, 2H), 4.06 (t, 2H, J=6Hz), 2.27-2.38 (m, 6H), 1.82-1.89 (m, 2H), 1.44-1.49 (m, 4H), 1.33-1.38 (m, 2H). IR (KBr, cm^{-1}) 2930, 2846, 2770, 1613, 1590, 1504, 1453, 1312, 1259, 1180, 1134, 1096, 1014, 955, 846, 807, 741, 702, 657. MS (ES^+) m/e 451. Anal. Calcd for $\text{C}_{24}\text{H}_{26}\text{N}_4\text{O}_3\text{S}$ C, 63.98; H, 5.82; N, 12.43. Found C, 63.95; H, 5.79; N, 12.35. Mp($^\circ\text{C}$)=108.

20

Example 231

- Preparation of 1-Methyl-2-{5-[4-(3-piperidin-1-yl-propoxy)phenyl]-[1,3,4]oxadiazol-2-ylmethylsulfanyl}-1*H*-benzimidazole



Method A: To a solution of 2-{5-[4-(3-piperidin-1-yl-propoxy)phenyl]-[1,3,4]oxadiazol-2-ylmethylsulfanyl}-1*H*-benzimidazole (0.066 g, 0.15 mmol) in 3 ml DMF at room temperature was added potassium carbonate (0.022 g, 0.15 mmol),

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tertbutylammonium bromide (0.005 g, 0.02 mmol) and dimethyl sulfate (0.019 g, 0.15 mmol). The reaction was stirred at room temperature for 5 days.

Method B: To a suspension of 2-{5-[4-(3-piperidin-1-yl-propoxy)phenyl]-[1,3,4]oxadiazol-2-ylmethylsulfanyl}-1*H*-benzimidazole (0.052 g, 0.12 mmol) in 3 ml acetone was added potassium carbonate (0.018 g, 0.135 mmol), tertbutylammonium bromide (0.004 g, 0.01 mmol) and dimethyl sulfate (0.015 g, 0.12 mmol). The reaction was stirred at room temperature for 6 days.

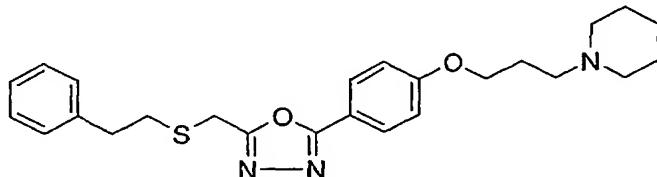
The reactions were combined and diluted with 25 ml H₂O then extracted with EtOAc (2 x 25 ml). The organic phases were combined, washed with brine, dried over Na₂SO₄, filtered, concentrated to an oil. Purification by radial chromatography on silica gel (eluted with 5% 2M NH₃ in MeOH:CH₂Cl₂) followed by conversion to the di-HCl salt as described in Example 5 using the acetyl chloride/EtOH method to generate HCl *in situ* afforded 0.016 g (14%) of 1-methyl-2-{5-[4-(3-piperidin-1-yl-propoxy)phenyl]-[1,3,4]oxadiazol-2-ylmethylsulfanyl}-1*H*-benzimidazole.

¹H NMR (DMSO-d6) δ 7.83 (d, 2H), 7.51-7.55 (m, 2H), 7.14-7.25 (m, 2H), 7.08 (d, 2H), 4.90 (s, 2H), 4.14 (t, 2H), 3.73 (s, 3H), 3.41-3.49 (m, 2H), 3.14-3.21 (m, 2H), 2.81-2.93 (m, 2H), 2.14-2.23 (m, 2H), 1.65-1.83 (m, 5H), 1.31-1.45 (m, 1H). MS (ES⁺) m/e 464. Mp(°C)=194.

20

Example 232

Preparation of Dimethyl-{3-[4-(5-phenethylsulfanylmethyl-[1,3,4]oxadiazol-2-yl)phenoxy]propyl} amine



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 193c from thiobenzoic acid *S*-(2-{N'-[4-(3-dimethylamino propoxy)benzoyl]hydrazino}-2-oxoethyl)ester (0.205 g, 0.5 mmol), (2-bromoethyl) benzene (0.095 g, 0.5 mmol) and lithium hydroxide (0.025 g, 1.0 mmol) to afford 0.139 g (62%) of dimethyl-{3-[4-(5-phenethylsulfanylmethyl-[1,3,4]oxadiazol-2-yl)phenoxy] propyl} amine as the hydrochloride salt.

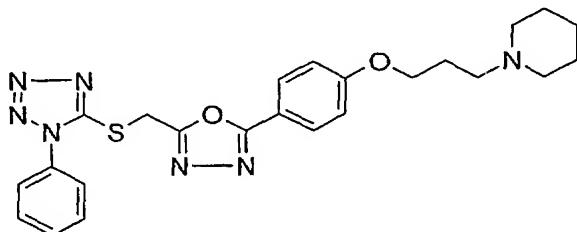
-424-

¹H NMR (DMSO-d6) δ 7.90 (d, 2H, J=9 Hz), 7.05-7.23 (m, 7H), 4.15 (t, 2H, J=6 Hz), 4.10 (s, 2H), 3.16-3.22 (m, 2H), 2.86 (s, 4H), 2.79 (s, 6H), 2.09-2.17 (m, 2H). MS (ES⁺) m/e 398. Analytical HPLC: 100%. Anal. Calcd for C₂₂H₂₇N₃O₂S HCl C, 60.89; H, 6.50; N, 9.68. Found C, 60.64; H, 6.47; N, 9.67. Mp(°C)=Decomposes at 173.

5

Example 233

Preparation of 1-(3-{4-[5-Phenyl-1*H*-tetrazol-5-yl-sulfanylmethyl)-[1,3,4] oxadiazol-2-yl]phenoxy}propyl)piperidine

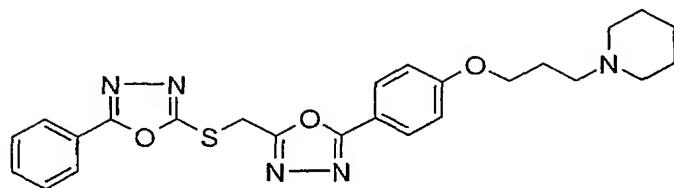


10 The above compound was prepared in a manner similar to that exemplified for the preparation of Example 28 from 1-phenyl-1*H*-tetrazole (0.146 g, 0.82 mmol), 1-{3-[4-(5-chloromethyl-[1,3,4]oxadiazol-2-yl)phenoxy] propyl}piperidine (0.250 g, 0.74 mmol) and sodium hydride (0.033g, 0.82 mmol) to afford 0.244 g (64%) of 1-(3-{4-[5-Phenyl-1*H*-tetrazol-5-yl-sulfanylmethyl)-[1,3,4] oxadiazol-2-yl]phenoxy}propyl)piperidine as the hydrochloride salt.

15 ¹H NMR (DMSO-d6) δ 7.85 (d, 2H, J=9Hz), 7.63 (s, 5H), 4.88 (s, 2H), 4.15 (t, 2H, J=6Hz), 3.41-3.48 (m, 2H), 3.12-3.21 (m, 2H), 2.81-2.92 (m, 2H), 2.12-2.22 (m, 2H), 1.63-1.83 (m, 5H), 1.31-1.41 (m, 1H). IR (KBr, cm⁻¹) 2946, 2621, 2499, 2407, 1615, 1499, 1390, 1309, 1252, 1390, 1309, 1252, 1173, 1066, 1015, 838, 767, 738, 696. MS (ES⁺) m/e 451. Analytical HPLC: 100%. Anal. Calcd for C₂₄H₂₇N₇O₂S HCl C, 56.08; H, 5.49; N, 19.07. Found C, 56.02; H, 5.509; N, 18.86. Mp(°C)=Decomposes at 182.

Example 234

Preparation of 1-(3-{4-[5-(5-Phenyl-[1,3,4]oxadiazol-2-yl-sulfanylmethyl)-[1,3,4] oxadiazol-2-yl]phenoxy}propyl)piperidine



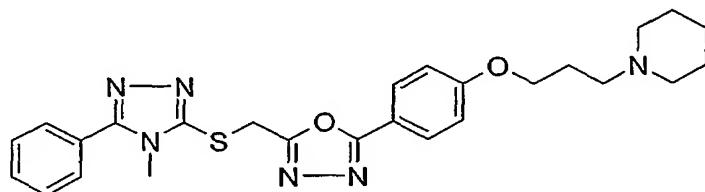
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 220 from 5-phenyl-1,3,4-oxadiazole-2-thiol (0.146 g, 0.82 mmol), 1-{3-[4-(5-chloromethyl-[1,3,4]oxadiazol-2-yl)phenoxy] propyl}piperidine (0.250 g, 0.74 mmol) and sodium hydride (0.033g, 0.82 mmol) to afford 0.259 g (73%) of 1-(3-{4-[5-(5-Phenyl-[1,3,4]oxadiazol-2-yl-sulfanylmethyl)-[1,3,4] oxadiazol-2-yl]phenoxy} propyl)piperidine.

¹H NMR (DMSO-d₆) δ 7.94 (d, 2H, J=8Hz), 7.82 (d, 2H, J=9Hz), 7.54-7.64 (m, 3H), 7.07 (d, 2H, J=9Hz), 4.89 (s, 2H), 4.07 (t, 2H, J= 6Hz), 2.21-2.42 (m, 6H), 1.80-1.91 (m, 2H), 1.41-1.51 (m, 4H), 1.29-1.40 (m, 2H). IR (KBr, cm⁻¹) 3067, 2929, 2851, 2752, 1609, 1570, 1480, 1416, 1303, 1253, 1179, 1125, 1065, 1021, 988, 955, 848, 741, 704. MS (ES⁺) m/e 478, MS (ES⁻) m/e 476. Anal. Calcd for C₂₅H₂₇N₅O₃S C, 62.87; H, 5.70; N, 14.66. Found C, 62.75; H, 5.63; N, 14.53. Mp(°C)=118.

15

Example 235

Preparation of 1-(3-{4-[5-(4-methyl-5-phenyl-4H-[1,2,4]triazol-3-ylsulfanylmethyl)-[1,3,4] oxadiazol-2-yl]phenoxy}propyl)piperidine



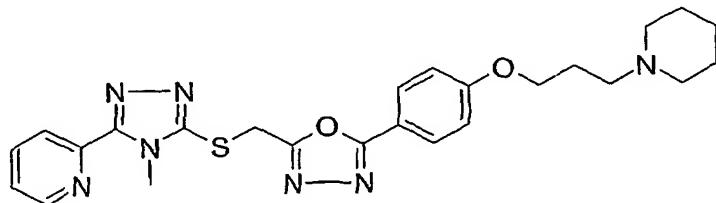
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 220 from 4-methyl-5-phenyl-4H-[1,2,4]triazole-3-thiol (0.157 g, 0.82 mmol), 1-{3-[4-(5-chloromethyl-[1,3,4]oxadiazol-2-yl)phenoxy] propyl}piperidine (0.250 g, 0.74 mmol) and sodium hydride (0.033g, 0.82 mmol) to afford 0.132 g (34%) of 1-(3-{4-[5-(4-methyl-5-phenyl-4H-[1,2,4]triazol-3-ylsulfanylmethyl)-[1,3,4] oxadiazol-2-yl]phenoxy}propyl)piperidine as the hydrochloride salt.

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¹H NMR (DMSO-d₆) δ 7.84 (d, 2H, J=9Hz), 7.65-7.70 (m, 2H), 7.53-7.57 (m, 3H), 7.10 (d, 2H, J=9Hz), 4.68 (s, 2H), 4.14 (t, 2H, J=6Hz), 3.40-3.48 (m, 2H), 3.12-3.20 (m, 2H), 2.81-2.91 (m, 2H), 2.15-2.23 (m, 2H), 1.65-1.81 (m, 5H), 1.32-1.40 (m, 1H). IR (KBr, cm⁻¹) 3420, 2944, 2623, 2514, 1615, 1501, 1472, 1398, 1252, 1179, 1068, 942, 5 842, 777, 705. MS (ES⁺) m/e 489. Analytical HPLC: 100%. Mp(°C)=Decomposes at 174.

Example 236

Preparation of 2-(4-Methyl-5-{5-[4-(3-piperidin-1-yl-propoxy)phenyl]-[1,3,4]oxadiazol-2-ylmethylsulfanyl}-4H-[1,2,4]triazol-3-yl)pyridine



10

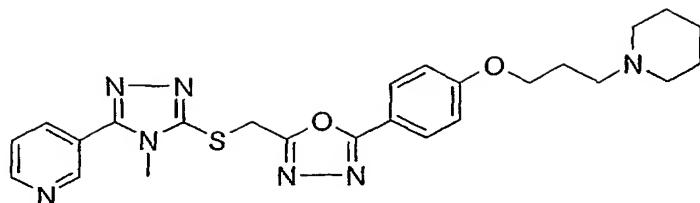
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 220 from 4-methyl-5-pyridin-2-yl-4H-[1,2,4]triazole-3-thiol (0.157 g, 0.82 mmol), 1-{3-[4-(5-chloromethyl-[1,3,4]oxadiazol-2-yl)phenoxy]propyl}piperidine (0.250 g, 0.74 mmol) and sodium hydride (0.033g, 0.82 mmol) to afford 0.161 g (41%) of 2-(4-Methyl-5-{5-[4-(3-piperidin-1-yl-propoxy)phenyl]-[1,3,4]oxadiazol-2-ylmethylsulfanyl}-4H-[1,2,4]triazol-3-yl)pyridine as the dihydrochloride salt.

15 ¹H NMR (DMSO-d₆) δ 8.70 (d, 1H, J=4Hz), 8.11 (d, 1H, J=8Hz), 7.97-8.02 (m, 1H), 7.83 (d, 2H, J=9Hz), 7.51-7.54 (m, 1H), 7.07 (d, 2H, J=9Hz), 4.69 (s, 2H), 4.15 (t, 2H, J=6Hz), 3.42-3.49 (m, 2H), 3.14-3.21 (m, 2H), 2.82-2.91 (m, 2H), 2.13-2.20 (m, 2H), 1.76-1.84 (m, 2H), 1.65-1.73 (m, 3H), 1.34-1.40 (m, 1H). IR (KBr, cm⁻¹) 3420, 2948, 2619, 2498, 1829, 1613, 1569, 1500, 1469, 1307, 1255, 1176, 1084, 945, 837, 795, 738, 709. MS (ES⁺) m/e 491. Analytical HPLC: 100%. Mp(°C)=112.

25

Example 237

Preparation of 3-(4-Methyl-5-{5-[4-(3-piperidin-1-yl-propoxy)phenyl]-[1,3,4]oxadiazol-2-ylmethylsulfanyl}-4H-[1,2,4]triazol-3-yl)pyridine



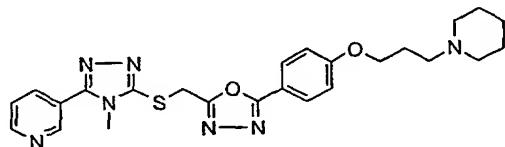
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 220 from 4-methyl-5-pyridin-3-yl-4H-[1,2,4]triazole-3-thiol (0.157 g, 0.82 mmol), 1-{3-[4-(5-chloromethyl-[1,3,4]oxadiazol-2-yl)phenoxy}propyl)piperidine (0.250 g, 0.74 mmol) and sodium hydride (0.033g, 0.82 mmol) to afford 0.138 g (38%) of 3-(4-Methyl-5-{5-[4-(3-piperidin-1-yl-propoxy)phenyl]-[1,3,4]oxadiazol-2-ylmethylsulfanyl}-4H-[1,2,4]triazol-3-yl)pyridine.

¹H NMR (DMSO-d₆) δ 8.87 (s, 1H), 8.72 (d, 1H, J=5Hz), 7.81 (d, 1H, J=9Hz), 7.57-7.60 (m, 1H), 7.08 (d, 2H, J=9Hz), 4.70 (s, 2H), 4.07 (t, 2H, J=6Hz), 2.26-2.39 (m, 6H), 1.82-1.89 (m, 2H), 1.42-1.52 (m, 4H), 1.30-1.40 (m, 2H). IR (KBr, cm⁻¹) 2932, 2761, 1614, 1569, 1500 1422, 1367, 1301, 1255, 1176, 1158, 1093, 1028, 856, 818, 712. MS (ES⁺) m/e 492, MS (ES⁻) m/e 490. Analytical HPLC: 100%. Anal. Calcd for C₂₅H₂₉N₇O₂S C, 61.08; H, 5.95; N, 19.94. Found C, 60.93; H, 5.94; N, 19.71. Mp(°C)=118.

15

Example 238

Preparation of 1-(3-{4-[5-Phenyl-1*H*-imidazol-2-ylsulfanyl methyl-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)piperidine



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 220 from 1-phenyl-1*H*-imidazole-2-thiol (0.144 g, 0.82 mmol), 1-{3-[4-(5-chloromethyl-[1,3,4]oxadiazol-2-yl)phenoxy}propyl)piperidine (0.250 g, 0.74 mmol) and sodium hydride (0.033g, 0.82 mmol) to afford 0.295 g (77%) of 1-(3-{4-[5-Phenyl-1*H*-imidazol-2-ylsulfanyl methyl-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)piperidine as the dihydrochloride salt.

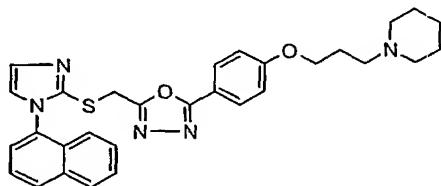
-428-

¹H NMR (DMSO-d₆) δ 7.76-7.84 (m, 3H), 7.59 (s, 1H), 7.35-7.48 (m, 5H), 7.13 (d, 2H, J=9Hz), 4.56 (s, 2H), 4.16 (t, 2H, J=6Hz), 3.41-3.48 (m, 2H), 3.13-3.20 (m, 2H), 2.81-2.92 (m, 2H), 2.18-2.27 (m, 2H), 1.74-1.83 (m, 4H), 1.66-1.73 (m, 1H), 1.33-1.43 (m, 1H). IR (KBr, cm⁻¹) 3415, 3162, 2944, 2681, 2490, 1731, 1612, 1567, 1500, 1430, 1373, 1304, 1254, 1180, 1088, 1008, 845, 758, 697. MS (ES⁺) m/e 476.

5 Mp(°C)=Decomposes at 177.

Example 239

Preparation of 1-(3-{4-[5-(1-Naphthalen-1-yl-1*H*-imidazol-2-ylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)piperidine



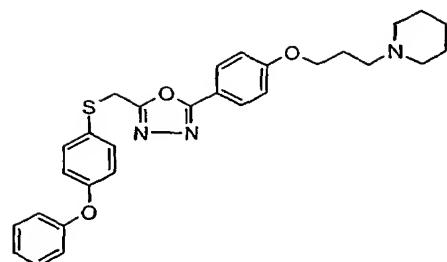
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 220 from 1-naphthalene-1yl-1*H*-imidazole-2-thiol (0.185 g, 0.82 mmol), 1-{3-[4-(5-chloromethyl-[1,3,4]oxadiazol-2-yl)phenoxy] propyl}piperidine (0.250 g, 0.74 mmol) and sodium hydride (0.033g, 0.82 mmol) to afford 0.358 g (86%) of 1-(3-{4-[5-(1-Naphthalen-1-yl-1*H*-imidazol-2-ylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)piperidine as the dihydrochloride salt.

¹H NMR (DMSO-d₆) δ 8.10 (d, 1H, J=7Hz), 8.03 (d, 1H, J=8Hz), 7.75-7.80 (m, 3H), 7.48-7.59 (m, 4H), 7.34-7.39 (m, 1H), 7.13 (d, 2H, J=9Hz), 7.05 (d, 1H, J=8Hz), 4.40-4.60 (m, 2H), 4.18 (t, 2H, J=6Hz), 3.42-3.48 (m, 2H), 3.14-3.21 (m, 2H), 2.82-2.92 (m, 2H), 2.17-2.25 (m, 2H), 1.67-1.82 (m, 5H), 1.34-1.42 (m, 1H). IR (KBr, cm⁻¹) 3416, 3058, 2944, 2638, 2538, 1612, 1568, 1499, 1474, 1397, 1304, 1255, 1176, 1086, 1017, 841, 807, 776. MS (ES⁺) m/e 526. Anal. Calcd for C₃₀H₃₁N₅O₂S 2HCl C, 60.20; H, 5.57; N, 11.70. Found C, 60.08; H, 5.63; N, 11.49. Mp(°C)=Decomposes at 120.

25

Example 240

Preparation of 1-(3-{4-[5-(4-Phenoxyphenylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenoxy} propyl)piperidine



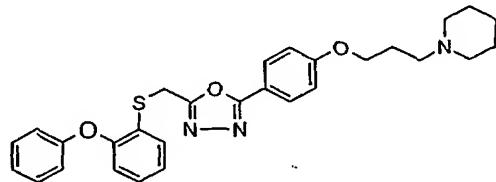
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 220 from 4-phenoxybenzene thiol (0.166 g, 0.82 mmol), 1-{3-[4-(5-chloromethyl-[1,3,4]oxadiazol-2-yl)phenoxy] propyl}piperidine (0.250 g, 0.74 mmol) and sodium hydride (0.033g, 0.82 mmol) to afford 0.161 g (40%) of 1-(3-{4-[5-(4-phenoxyphenylsulfanyl)methyl]-[1,3,4]oxadiazol-2-yl}phenoxy) propyl)piperidine as the hydrochloride salt.

¹H NMR (DMSO-d₆) δ 7.82 (d, 2H, J=9Hz), 7.45 (d, 2H, J=9Hz), 7.34-7.39 (m, 2H), 7.09-7.16 (m, 3H), 6.93-7.00 (m, 4H), 4.48 (s, 2H), 4.15 (t, 2H, J=6Hz), 3.41-3.48 (m, 2H), 3.13-3.20 (m, 2H), 2.82-2.91 (m, 2H), 2.15-2.22 (m, 2H), 1.65-1.83 (m, 5H), 1.33-1.41 (m, 1H). IR (KBr, cm⁻¹) 2936, 2863, 2620, 2499, 2418, 1612, 1582, 1498, 1422, 1232, 1171, 1090, 1038, 1005, 961, 833, 758, 693, 503. MS (ES⁺) m/e 502. Anal. Calcd for C₂₉H₃₁N₃O₃S HCl C, 64.73; H, 5.99; N, 7.81. Found C, 64.49; H, 6.01; N, 7.75. Mp(°C)=169.

15

Example 241

1-(3-{4-[5-(2-Phenoxyphenylsulfanyl)methyl]-[1,3,4]oxadiazol-2-yl}phenoxy) propyl)piperidine



20 The above compound was prepared in a manner similar to that exemplified for the preparation of Example 220 from 2-phenoxybenzene thiol (0.166 g, 0.82 mmol), 1-{3-[4-(5-chloromethyl-[1,3,4]oxadiazol-2-yl)phenoxy] propyl}piperidine (0.250 g, 0.74 mmol) and sodium hydride (0.033g, 0.82 mmol) to afford 0.166 g (41%) of 1-(3-{4-[5-(4-

-430-

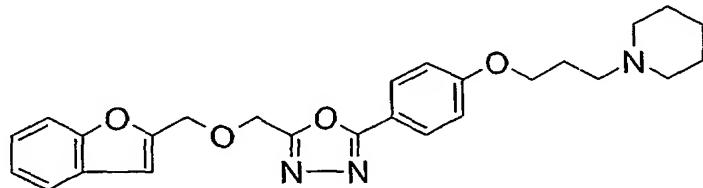
phenoxyphenylsulfanyl methyl)-[1,3,4]oxadiazol-2-yl]phenoxy} propyl)piperidine as the hydrochloride salt.

¹H NMR (DMSO-d₆) δ 7.79 (d, 2H, J=9Hz), 7.61 (dd, 1H, J=2, 8Hz), 7.25-7.31 (m, 3H), 7.15-7.19 (m, 1H), 7.03-7.12 (m, 3H), 6.90 (dd, 1H, J=2, 8Hz), 6.84 (d, 2H, J=7 Hz), 4.54 (s, 2H), 4.14 (t, 2H, J=6Hz), 3.42-3.48 (m, 2H), 3.14-3.19 (m, 2H), 2.82-2.91 (m, 2H), 2.14-2.21 (m, 2H), 1.66-1.82 (m, 5H), 1.43-1.42 (m, 1H). IR (KBr, cm⁻¹) 2949, 2618, 2488, 1612, 1570, 1499, 1470, 1298, 1253, 1230, 1175, 1069, 941, 834, 755. MS (ES⁺) m/e 502. Anal. Calcd for C₂₉H₃₁N₃O₃S HCl C, 64.73; H, 5.99; N, 7.81. Found C, 64.44; H, 5.94; N, 7.68. Mp(°C)=132.

10

Example 242

1-(3-{4-[5-(Benzofuran-2-ylmethoxymethyl)-[1,3,4]oxadiazol-2-yl]phenoxy} propyl)piperidine



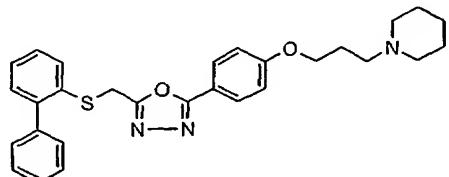
15 The above compound was prepared in a manner similar to that exemplified for the preparation of Example 202b from {5-[4-(3-piperidin-2-yl-propoxy)phenyl] [1,3,4] oxadiazol-2-yl}methanol (0.216 g, 0.7mmol), 2-chloromethlybenzofuran (0.113 g, 0.7 mmol) and sodium hydride (0.027 g, 0.7 mmol). Purification by radial chromatography (eluted with 5% NH₃ in MeOH:CH₂Cl₂) afforded 0.129 g of the title compound as an oil that slowly crystallizes out. This material was combined with 0.021 g from a previous run, then converted to the HCl salt as described in Example 5 using the acetyl chloride/ EtOH method to generate HCl *in situ* afforded 0.091 g of 1-(3-{4-[5-(benzofuran-2-ylmethoxymethyl)-[1,3,4]oxadiazol-2-yl]phenoxy}propyl)piperidine.

20 ¹H NMR (DMSO-d₆) δ 7.88 (d, 2H), 7.81 (d, 1H), 7.73 (d, 1H), 7.20-7.33 (m, 2H), 7.11 (d, 2H), 6.95 (s, 1H), 4.86 (s, 2H), 4.79 (s, 2H), 4.15 (t, 2H), 3.43-3.50 (m, 2H), 3.15-3.23 (m, 2H), 2.83-2.94 (m, 2H), 2.15-2.23 (m, 2H), 1.65-1.85 (m, 5H), 1.33-1.45 (m, 1H). MS (ES⁺) m/e 448. Mp(°C)=138.

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Example 243

1-(3-{4-[5-(Biphenyl-2-ylsulfanyl)methyl]-[1,3,4]oxadiazol-2-yl}phenoxy) propyl)piperidine

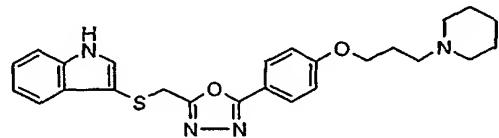


5 The above compound was prepared in a manner similar to that exemplified for the preparation of Example 220 from biphenyl-2-thiol (0.152 g, 0.82 mmol), 1-{3-[4-(5-chloromethyl-[1,3,4]oxadiazol-2-yl)phenoxy] propyl}piperidine (0.250 g, 0.74 mmol) and sodium hydride (0.033g, 0.82 mmol) to afford 0.213 g (55%) of 1-(3-{4-[5-(biphenyl-2-ylsulfanyl)methyl]-[1,3,4]oxadiazol-2-yl}phenoxy) propyl)piperidine as the hydrochloride salt.

10 ¹H NMR (DMSO-d6) δ 7.78 (d, 2H, J=9Hz), 7.66 (d, 1H, J=8Hz), 7.29-7.40 (m, 5H), 7.20-7.25 (m, 3H), 7.11 (d, 2H, J=9Hz), 4.39 (s, 2H), 4.15 (t, 2H, J=6Hz), 3.40-3.48 (m, 2H), 3.12-3.21 (m, 2H), 2.81-2.91 (m, 2H), 2.12-2.23 (m, 2H), 1.65-1.83 (m, 5H), 1.32-1.41 (m, 1H). IR (KBr, cm⁻¹) 3435, 3058, 2947, 2632, 2496, 1614, 1586, 1497, 1466, 1428, 1309, 1249, 1176, 1084, 1052, 839, 746, 700. MS (ES⁺) m/e 486. Analytical HPLC: 100%. Mp(°C)=165.

Example 244

20 3-{5-[4-(3-Piperidine-1-yl-propoxy)phenyl]-[1,3,4]oxadiazol-2-ylmethylsulfanyl}-1*H*-indole



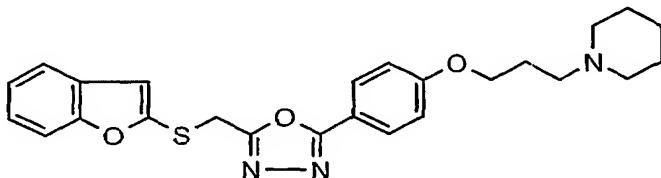
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 220 from 3-mercaptopindole (0.252 g, 1.69 mmol), 1-{3-[4-(5-chloromethyl-[1,3,4]oxadiazol-2-yl)phenoxy] propyl}piperidine (0.515 g, 1.53 mmol) and sodium hydride (0.067g, 1.69 mmol) to afford 0.2963 g (43%) of 3-{5-[4-(3-piperidine-1-yl-propoxy)phenyl]-[1,3,4]oxadiazol-2-ylmethylsulfanyl}-1*H*-indole.

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¹H NMR (DMSO-d₆) δ 7.767 (d, 2H, J= Hz), 7.38-7.47 (m, 3H), 7.04-7.11 (m, 3H), 6.93-6.97 (m, 1H), 4.12 (s, 2H), 4.07 (t, 2H, J=6Hz), 2.28-2.39 (m, 6H), 1.83-1.90 (m, 2H), 1.43-1.52 (m, 4H), 1.32-1.40 (m, 2H). IR (KBr, cm⁻¹) 3221, 3097, 2933, 2850, 2765, 1609, 1567, 1500, 1463, 1423, 1302, 1256, 1173, 1127, 1017, 839, 738. MS (ES⁺) m/e 449, MS (ES⁻) m/e 447. Mp(^oC)=155.

Example 245

1-(3-{4-[5-(Benzofuran-2-ylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenoxy} propyl)piperidine



10

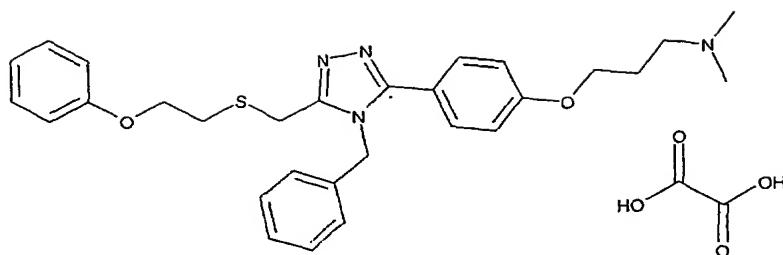
A suspension of 2-[1,2,3]thiazol-4-yl-phenol (0.0.082 g, 0.46 mmol), 1-{3-[4-(5-chloromethyl-[1,3,4]oxadiazol-2-yl)phenoxy] propyl}piperidine (0.154 g, 0.46 mmol) and potassium carbonate (0.076g, 0.55 mmol) was refluxed for 48 hours then concentrated to an oil. The oil was treated with H₂O then extracted twice with EtOAc. The combined organic phases were washed with brine, dried over Na₂SO₄, filtered, concentrated to an oil. Purification by radial chromatography on silica gel (eluted with 5% 2M NH₃ in MeOH:CH₂Cl₂) followed by conversion to the HCl salt as described in Example 5 using the acetyl chloride/ EtOH method to generate HCl *in situ* afforded 0.074 g (33%) of 1-(3-{4-[5-(benzofuran-2-ylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]phenoxy} propyl)piperidine as the hydrochloride salt.

¹H NMR (DMSO-d₆) δ 7.71 (d, 2H, J=9 Hz), 7.58 (d, 1H, J=7 Hz), 7.51 (d, 1H, J=7 Hz), 7.31-7.35 (m, 2H), 7.14 (s, 1H), 7.05 (d, 2H, J=9 Hz), 4.56 (s, 2H), 4.13 (t, 2H, J=6 Hz), 3.39-3.48 (m, 2H), 3.12-3.20 (m, 2H), 2.80-2.92 (m, 2H), 2.13-2.22 (m, 2H), 1.65-1.83 (m, 5H), 1.33-1.40 (m, 1H). IR (KBr, cm⁻¹) 2943, 2619, 2503, 1615, 1499, 1446, 1252, 1178, 1055, 944, 840, 750, 415. MS (ES⁺) m/e 450.

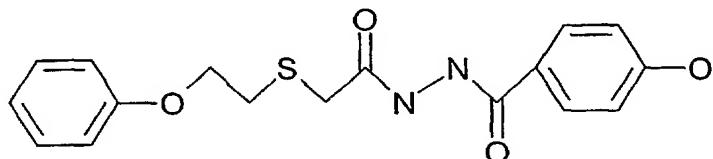
Example 246

Preparation of (3-{4-[4-benzyl-5-(2-phenoxyethylsulfanylmethyl)-4H-[1,2,4]triazol-3-yl]-phenoxy}-propyl)- dimethyl-amine, oxalic acid salt

-433-



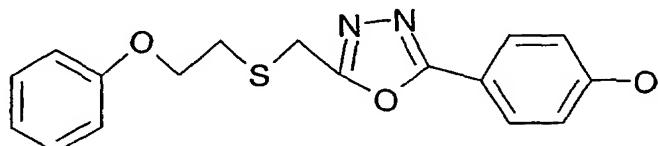
a) 4-Hydroxy-benzoic acid N'-[2-(2-phenoxy-ethylsulfanyl)-acetyl]-hydrazide



A solution of (2-phenoxy-ethylsulfanyl)-acetic acid (0.848 g, 4.0 mM) and (2-phenoxy-1-ethoxycarbonyl-1,2-dihydroquinoline, ethyl 1,2-dihydro-2-ethoxy-1-quinolinemcarboxylate),(EEDQ), (0.989 g, 4.0 mM) in 20 mL acetonitrile and 5 mL THF were stirred together at room temperature for 1 hr. 4-Hydroxy-benzoic acid hydrazide (0.608 g, 4.0 mM) was added and the mixture was sonicated for 2 hrs and stirred at room temperature for 16 hrs. The mixture was concentrated to low volume and extracted with ethyl acetate. The organic extract was washed with 1N HCl, H₂O, NaHCO₃, brine, dried over magnesium sulfate, filtered, and concentrated to dryness to give 1.28 g (92%) of 4-hydroxy-benzoic acid N'-[2-(2-phenoxy-ethylsulfanyl)-acetyl]-hydrazide.

¹H NMR (DMSO-d6) δ 10.2 (s, 1H), 10.1 (s, 1H), 10.0 (s, 1H), 7.7 (d, 2H, J=9 Hz), 7.3 (m, 2H), 6.9 (m, 3H), 6.8 (d, 2H, J=9 Hz), 4.2 (t, 2H, J=6 Hz), 3.3 (m, 2H), 3.0 (t, 2H, J=6 Hz). IR (KBr, cm⁻¹) 3305, 3201, 3003, 2918, 2867, 1696, 1623, 1609, 1584, 1517, 1287, 1242, 1229. MS (ESI) m/e 347, 345. Anal. Calcd for C₁₇H₁₈N₂O₄S: C, 58.95; H, 5.24; N, 8.09. Found C, 58.37; H, 5.51; N, 7.19.

b) 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol



20

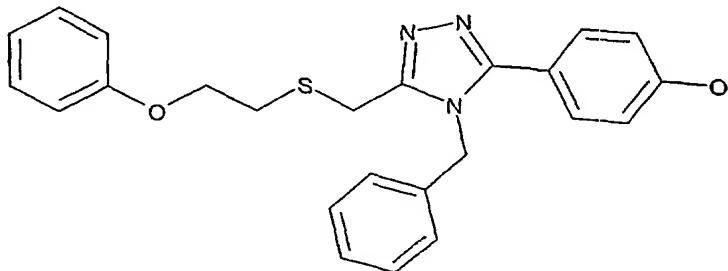
A solution of 4-hydroxy-benzoic acid N'-[2-(2-phenoxy-ethylsulfanyl)-acetyl]-hydrazide (4.87 g, 14.1 mM), triphenyl phosphine (7.38 g, 28.1 mM), and triethylamine

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(5.14 g, 50.7 mM) were stirred together in acetonitrile (15 mL). Carbon tetrachloride (9.17 g, 57.9 mM) was added and the mixture was stirred at room temperature for 3 hrs. The material was concentrated to low volume and diluted with hexane (100 mL), ethyl acetate (6 mL), and ethanol (25 mL). The mixture was sonicated for 5 minutes and a precipitate formed. The solid was collected and dried in vacuo (30°C). The solid was slurried with 1N HCl, collected and dried to give 3.149 g (68%) of the title compound.

5 ¹H NMR (DMSO-d₆) δ 7.8 (d, 2H, J=9 Hz), 7.2 (t, 2H, J=8 Hz), 6.9 (m, 5H), 4.2 (m, 4H), 3.0 (t, 2H, J=6 Hz). IR (KBr, cm⁻¹) 3410, 1762, 1611, 1601, 1498, 1242, 1226, 1174, 752. MS (ESI) m/e 329, 327. Anal. Calcd for C₁₇H₁₆N₂O₃S: C, 62.18; H, 4.91; N, 10 8.53. Found C, 61.99; H, 5.00; N, 7.92. M.P.=172-175°C.

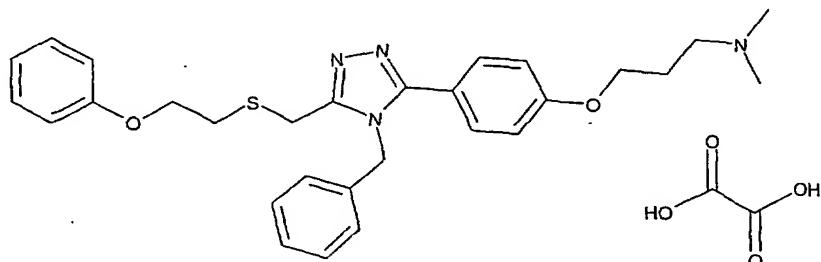
c) 4-[4-Benzyl-5-(2-phenoxyethylsulfanylmethyl)-4H-[1,2,4]triazol-3-yl]-phenol



A heterogeneous mixture of 4-[5-(2-phenoxyethylsulfanylmethyl)-15 [1,3,4]oxadiazol-2-yl]-phenol (0.657 g, 2.0 mM) in neat benzylamine (2.0 mL, 18.0 mM) was stirred at 120 °C for 18 h and at 150 °C for 6 h. The reaction mixture was allowed to cool to room temperature, diluted with ethyl acetate, and the organic layer washed with 1N HCl, water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to afford 0.903 g of a yellow gum. Purification by column chromatography on silica gel (isocratic elution with ethyl acetate) afforded 0.383 g (46%) 20 of 4-[4-Benzyl-5-(2-phenoxyethylsulfanylmethyl)-4H-[1,2,4]triazol-3-yl]-phenol as a white foam (MP 64-66 °C, MW 417.53).

1 ¹H NMR (DMSO-d₆) δ 9.87 (s, 1H), 7.32 (d, 2H, J=8 Hz), 7.27 (m, 5H), 6.92 (d, 2H, J=8 Hz), 6.88 (m, 3H), 6.78 (d, 2H, J=9 Hz), 5.34 (s, 2H), 4.07 (t, 2H, J=7 Hz), 3.92 (s, 2H), and 2.91 (t, 2H, J=7 Hz). IR (KBr, cm⁻¹) 3050-2470, 1612, 1496, 1453, 1282, 25 1241, 1172, 840, 754, and 692. MS (ESI) m/e 418, 416. Anal. Calcd for C₂₄H₂₃N₃O₂S: C, 69.04; H, 5.55; N, 10.06; S, 7.68. Found C, 68.39; H, 5.45; N, 9.77; S, 7.52.

d) (3-{4-[4-benzyl-5-(2-phenoxyethylsulfanylmethyl)-4H-[1,2,4]triazol-3-yl]-phenoxy}-propyl)- dimethyl-amine, oxalic acid salt



5 A heterogeneous mixture of 4-[4-Benzyl-5-(2-phenoxy-ethylsulfanylmethyl)-4H-[1,2,4]triazol-3-yl]-phenol (0.152 g, 0.36 mM), 3-chloro-N,N-dimethylpropylamine hydrochloride (0.063 g, 0.396 mM), and cesium carbonate (0.142 g, 0.432 mM) in 3 mL DMF was stirred at 90-100 °C for 7 h. Triton B (40 weight % in CH₃OH, 0.082 mL, 0.18 mM, 0.5 eq) was then added, and the reaction mixture heated at 90 °C for an additional 10 1.5 h. The reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate/H₂O. The solvent layers were separated, the aqueous layer back extracted with ethyl acetate, the combined organic extracts washed with water, saturated NaHCO₃ solution, 1N NaOH, and brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford 0.136 g of a yellow gum. Purification by column 15 chromatography on silica gel (isocratic elution with ethyl acetate followed by 9:1 CHCl₃/2.0 M ammonia in methanol) afforded 0.101 g (55%) of (3-{4-[4-benzyl-5-(2-phenoxyethylsulfanylmethyl)-4H-[1,2,4]triazol-3-yl]-phenoxy}-propyl)- dimethyl-amine as an oily gum. The gum (0.099 g, 0.196 mM) was dissolved in 2 mL acetone, and oxalic acid (0.019 g, 0.216 mM), dissolved in 1 mL acetone, was added with rapid stirring at 20 room temperature followed by the addition of diethyl ether/hexane (1:1, 2 mL). Filtered the resultant thick precipitate, washed the collected solid with acetone and diethyl ether, and dried in vacuo at 40 °C to afford 0.104 g (89%) of (3-{4-[4-benzyl-5-(2-phenoxyethylsulfanylmethyl)-4H-[1,2,4]triazol-3-yl]-phenoxy}-propyl)- dimethyl-amine, oxalic acid salt as an off-white solid (MP 88-92 °C, MW oxalate salt 592.72, MW free 25 amine 502.68).

¹H NMR (DMSO-d₆) δ 7.46 (d, 2H, J=9 Hz), 7.26 (m, 5H), 6.98 (d, 2H, J=9 Hz), 6.92 (m, 3H), 6.88 (d, 2H, J=9 Hz), 5.37 (s, 2H), 4.06 (m, 4H), 3.95 (s, 2H), 3.13 (m, 2H),

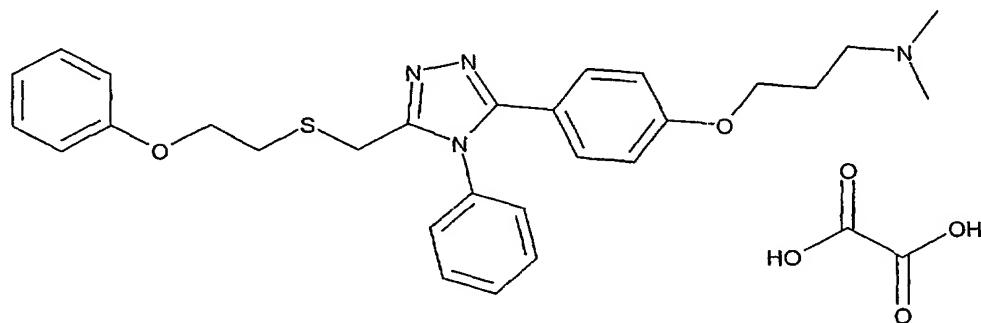
-436-

2.91 (t, 2H, $J=6$ Hz), 2.74 (s, 6H), and 2.06 (m, 2H). IR (KBr, cm^{-1}) 3037-2870, 2700-2500, 1721, 1611, 1478, 1248, 1176, 1036, 704, and 475. MS (ESI) m/e 503. Anal. Calcd for $\text{C}_{29}\text{H}_{34}\text{N}_4\text{O}_2\text{S} \cdot \text{C}_2\text{H}_2\text{O}_4$: C, 62.82; H, 6.12; N, 9.45; S, 5.41. Found C, 56.37; H, 5.27; N, 8.26; S, 5.37. Analytical HPLC: 88% purity.

5

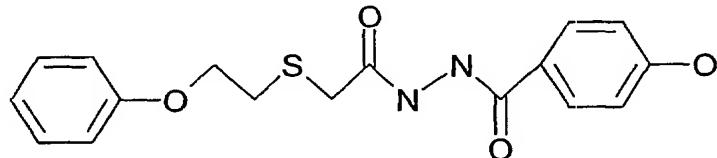
Example 247

Preparation of Dimethyl-(3-{4-[5-(2-phenoxy-ethylsulfanyl methyl)-4-phenyl-4H-[1,2,4]triazol-3-yl]-phenoxy}-propyl)-amine, oxalic acid salt



10

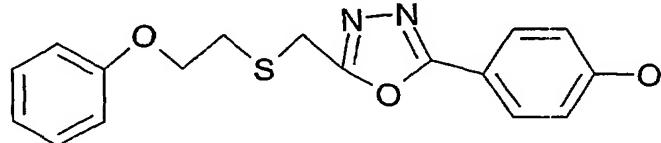
- a) 4-Hydroxy-benzoic acid N'-[2-(2-phenoxyethylsulfanyl)-acetyl]-hydrazide



The above compound was prepared in an identical manner as exemplified in Example 246a.

15

- b) 4-[5-(2-phenoxy-ethylsulfanyl methyl)-[1,3,4]oxadiazol-2-yl]-phenol

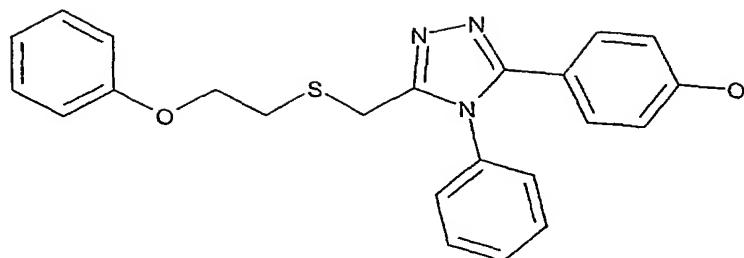


The above compound was prepared in an identical manner as exemplified in Example 246b.

20

- c) 4-[5-(2-Phenoxy-ethylsulfanyl methyl)-4-phenyl-4H-[1,2,4]triazol-3-yl]-phenol

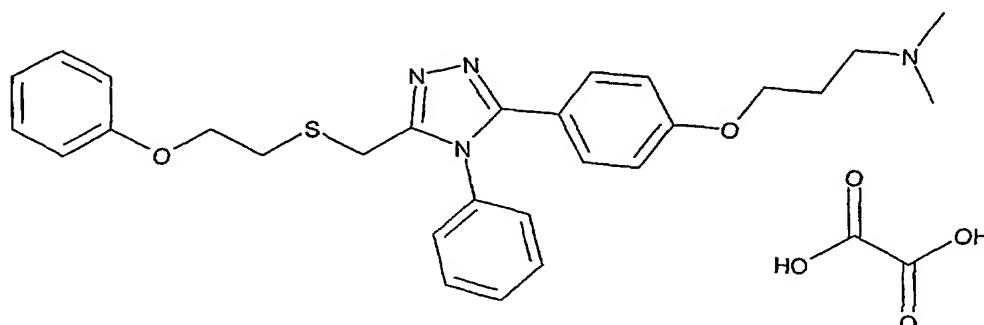
-437-



A heterogeneous mixture of 4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.985 g, 3.0 mM) in neat aniline (2.0 mL, 22.0 mM) was stirred at 150 °C for 12 h. The reaction mixture was allowed to cool to room temperature, 5 diluted with ethyl acetate, and the organic layer washed with 1N HCl, water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to afford a light tan solid. Added ethyl acetate and diethyl ether to the solid, sonicated, filtered, washed the collected solid with ethyl acetate and diethyl ether, and dried in vacuo at 40 °C to afford 0.99 g (82%) of 4-[5-(2-Phenoxy-ethylsulfanylmethyl)-4-phenyl-4H-10 [1,2,4]triazol-3-yl]-phenol as a light lavender solid (MP 214-216 °C, MW 403.51).

¹H NMR (DMSO-d₆) δ 9.83 (s, 1H), 7.51 (m, 3H), 7.38 (m, 2H), 7.26 (t, 2H, J=7 Hz), 7.12 (d, 2H, J=9 Hz), 6.91 (t, 1H, J=7 Hz), 6.87 (d, 2H, J=10 Hz), 6.66 (d, 2H, J=9 Hz), 4.02 (t, 2H, J=6 Hz), 3.80 (s, 2H), and 2.85 (t, 2H, J=7 Hz). IR (KBr, cm⁻¹) 3050-2487, 1607, 1585, 1499, 1469, 1285, 1244, 1176, 1037, and 691. MS (ESI) m/e 404, 402. 15 Anal. Calcd for C₂₃H₂₁N₃O₂S: C, 68.46; H, 5.25; N, 10.41; S, 7.95. Found C, 68.58; H, 5.26; N, 10.40; S, 7.94.

d) Dimethyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-4-phenyl-4H-[1,2,4]triazol-3-yl]-phenoxy}-propyl)-amine, oxalic acid salt



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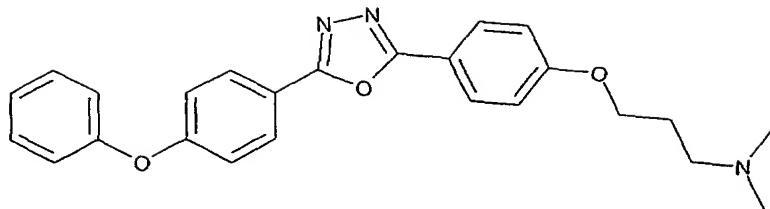
A heterogeneous mixture of 4-[5-(2-Phenoxy-ethylsulfanyl methyl)-4-phenyl-4H-[1,2,4]triazol-3-yl]-phenol (0.161 g, 0.4 mM), 3-chloro-N,N-dimethylpropylamine hydrochloride (0.07 g, 0.44 mM), and Triton B (40 weight % in CH₃OH, 0.418 mL, 0.92 mM) in 3 mL DMF was stirred at 90 °C for 4.5 h. Cesium carbonate (0.099 g, 0.3 mM, 5 0.75 eq) was then added, and the reaction mixture heated at 90 °C for an additional 2.5 h. The reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate/H₂O. The solvent layers were separated, the aqueous layer back extracted with ethyl acetate, the combined organic extracts washed with water, saturated NaHCO₃ solution, 1N NaOH, and brine, dried over anhydrous sodium sulfate, filtered, and 10 concentrated in vacuo to afford 0.155 g of a lavender gum. Purification by column chromatography on silica gel (isocratic elution with ethyl acetate followed by 95:5 CHCl₃/2.0 M ammonia in methanol) afforded 0.137 g (70%) of Dimethyl-(3-{4-[5-(2-phenoxy-ethylsulfanyl methyl)-4-phenyl-4H-[1,2,4]triazol-3-yl]-phenoxy}-propyl)-amine as an off-white. The gum (0.135 g, 0.276 mM) was dissolved in 2 mL acetone, and oxalic 15 acid (0.028 g, 0.304 mM), dissolved in 1 mL acetone, was added with rapid stirring at room temperature followed by the addition of diethyl ether/hexane (1:2, 3 mL). Filtered the resultant thick precipitate, washed the collected solid with diethyl ether and hexane, and dried in vacuo at 40 °C to afford 0.153 g (96%) of Dimethyl-(3-{4-[5-(2-phenoxy-ethylsulfanyl methyl)-4-phenyl-4H-[1,2,4]triazol-3-yl]-phenoxy}-propyl)-amine, oxalic 20 acid salt as a white solid (MP 120-123 °C, MW oxalate salt 578.70, MW free amine 488.66).

¹H NMR (DMSO-d₆) δ 7.51 (m, 3H), 7.41 (m, 2H), 7.34 (m, 2H), 7.25 (d, 2H, J=9 Hz), 6.91 (t, 1H, J=7 Hz), 6.88 (d, 2H, J=9 Hz), 6.87 (d, 2H, J=7 Hz), 4.01 (m, 4H), 3.81 (s, 2H), 3.10 (m, 2H), 2.86 (t, 2H, J=6 Hz), 2.72 (s, 6H), and 2.03 (m, 2H). IR (KBr, cm⁻¹) 2950-2870, 2700-2500, 1612, 1600, 1586, 1497, 1477, 1403, 1258, 1246, 1181, 704, and 694. MS (ESI) m/e 489. Anal. Calcd for C₂₈H₃₂N₄O₂S·C₂H₂O₄: C, 62.27; H, 5.92; N, 9.68; S, 5.54. Found C, 60.86; H, 5.40; N, 9.40; S, 5.61. Analytical HPLC: 94% purity.

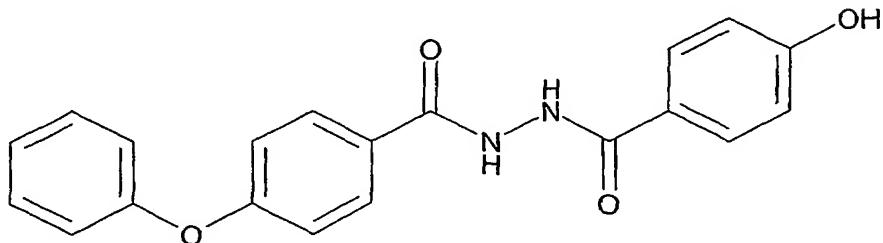
Example 248

30 Preparation of Dimethyl-(3-{4-[5-(4-phenoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine

-439-



a) 4-Hydroxy-benzoic acid N'-(4-phenoxy-benzoyl)-hydrazide

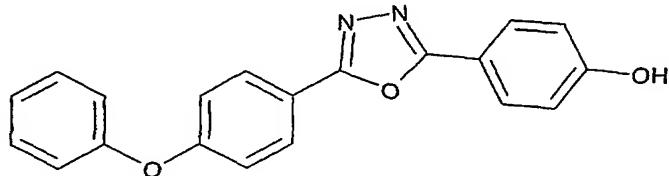


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 51a, from 4-phenoxybenzoic acid (1.09 g, 5.0 mM) to afford 1.01 g (58%) of 4-Hydroxy-benzoic acid N'-(4-phenoxy-benzoyl)-hydrazide as a white solid (MP 203-205 °C, MW 348.36).

¹H NMR (DMSO-d₆) δ 10.32 (s, 1H), 10.19 (s, 1H), 10.08 (s, 1H), 7.93 (d, 2H, J=9 Hz), 7.78 (d, 2H, J=9 Hz), 7.44 (t, 2H, J=8 Hz), 7.22 (t, 1H, J=8 Hz), 7.10 (d, 2H, J=8 Hz), 7.06 (d, 2H, J=9 Hz), and 6.83 (d, 2H, J=9 Hz). IR (KBr, cm⁻¹) 3216, 1656, 1614, 1586, 1573, 1515, 1488, 1284, 1247, 1169, 844, 753, and 693. MS (ESI) m/e 349, 347. Anal. Calcd for C₂₀H₁₆N₂O₄: C, 68.96; H, 4.63; N, 8.04. Found C, 68.65; H, 4.68; N, 8.00.

b) 4-[5-(4-phenoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-phenol

15

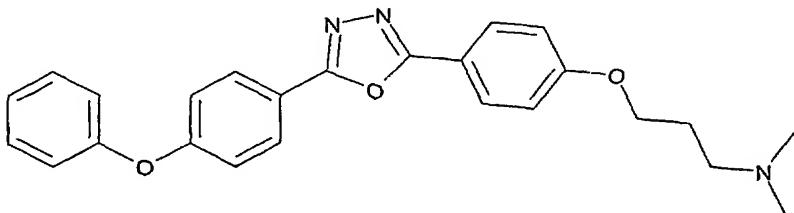


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 49e, from 4-hydroxy-benzoic acid N'-(4-phenoxy-benzoyl)-hydrazide (1.01 g, 2.9 mM), triphenylphosphine (1.54 g, 5.8 mM), and triethylamine (1.46 mL, 10.44 mM) to afford 0.65 g (68%) of 4-[5-(4-phenoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-phenol as a white solid (MP 204-206 °C, MW 330.35).

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¹H NMR (DMSO-d₆) δ 10.31 (s, 1H), 8.07 (d, 2H, J=9 Hz), 7.92 (d, 2H, J=9 Hz), 7.45 (t, 2H, J=8 Hz), 7.23 (t, 1H, J=7 Hz), 7.15 (d, 2H, J=9 Hz), 7.13 (d, 2H, J=9 Hz), and 6.95 (d, 2H, J=9 Hz). IR (KBr, cm⁻¹) 3125, 1740, 1612, 1588, 1492, 1379, 1287, 1240, 1167, 1099, 1068, 868, 847, 746, 695, and 510. MS (ESI) m/e 331, 329. Anal. Calcd for C₂₀H₁₄N₂O₃: C, 72.72; H, 4.27; N, 8.48. Found C, 70.35; H, 4.66; N, 7.27.

c) Dimethyl-(3-{4-[5-(4-phenoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine



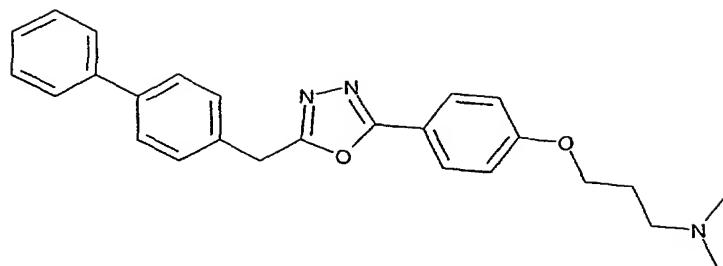
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 50f, from 4-[5-(4-phenoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.298 g, 0.9 mM) and purified by Chromatotron radial chromatography on silica gel (isocratic elution with 95:5 CH₂Cl₂/2.0 M ammonia in methanol) to afford 0.295 g (78%) of Dimethyl-(3-{4-[5-(4-phenoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine as a white solid (MP 95 °C, MW 415.50).

¹H NMR (CDCl₃) δ 8.07 (d, 2H, J=9 Hz), 8.04 (d, 2H, J=9 Hz), 7.40 (t, 2H, J=8 Hz), 7.20 (t, 1H, J=8 Hz), 7.10 (d, 2H, J=9 Hz), 7.09 (d, 2H, J=9 Hz), 7.02 (d, 2H, J=9 Hz), 4.12 (t, 2H, J=6 Hz), 2.61 (t, 2H, J=7 Hz), 2.38 (s, 6H), and 2.08 (m, 2H). IR (KBr, cm⁻¹) 2954, 2821, 2764, 1610, 1488, 1417, 1298, 1246, 1171, 1068, 996, 871, 835, 742, 689, 670, and 510. MS (ESI) m/e 416. Anal. Calcd for C₂₅H₂₅N₃O₃: C, 72.27; H, 6.06; N, 10.11. Found C, 71.99; H, 6.29; N, 9.94. Analytical HPLC: 100% purity.

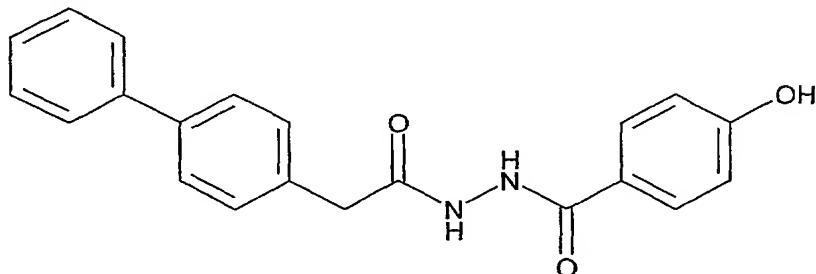
Example 249

Preparation of {3-[4-(5-Biphenyl-4-yl-methyl-[1,3,4]oxadiazol-2-yl)-phenoxy]-propyl}-dimethyl-amine

-441-



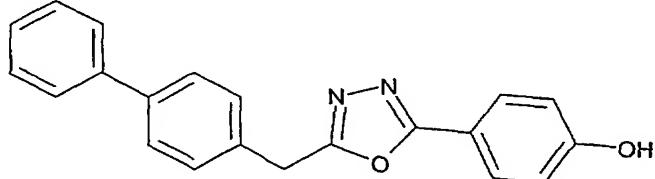
a) 4-Hydroxy-benzoic acid N'-(2-biphenyl-4-yl-acetyl)-hydrazide



The above compound was prepared in a manner similar to that exemplified for the
5 preparation of Example 51a, from 4-biphenylacetic acid (1.08 g, 5.0 mM) to afford 1.58 g
(91%) of 4-Hydroxy-benzoic acid N'-(2-biphenyl-4-yl-acetyl)-hydrazide as a white solid
(MP 234-239 °C dec, MW 346.13).

¹H NMR (DMSO-d₆) δ 10.10 (s, 1H), 10.09 (s, 1H), 10.05 (s, 1H), 7.73 (d, 2H,
J=9 Hz), 7.64 (d, 2H, J=7 Hz), 7.60 (d, 2H, J=8 Hz), 7.44 (t, 2H, J=8 Hz), 7.43 (d, 2H,
J=8 Hz), 7.34 (t, 1H, J=7 Hz), 6.80 (d, 2H, J=9 Hz), and 3.56 (s, 2H). IR (KBr, cm⁻¹)
10 3265, 1663, 1605, 1572, 1485, 1281, 1230, 847, 740, and 497. MS (ESI) m/e 347, 345.
Anal. Calcd for C₂₁H₁₈N₂O₃: C, 72.82; H, 5.24; N, 8.09. Found C, 71.83; H, 5.35; N,
8.31.

b) 4-(5-Biphenyl-4-yl-methyl-[1,3,4]oxadiazol-2-yl)-phenol



15

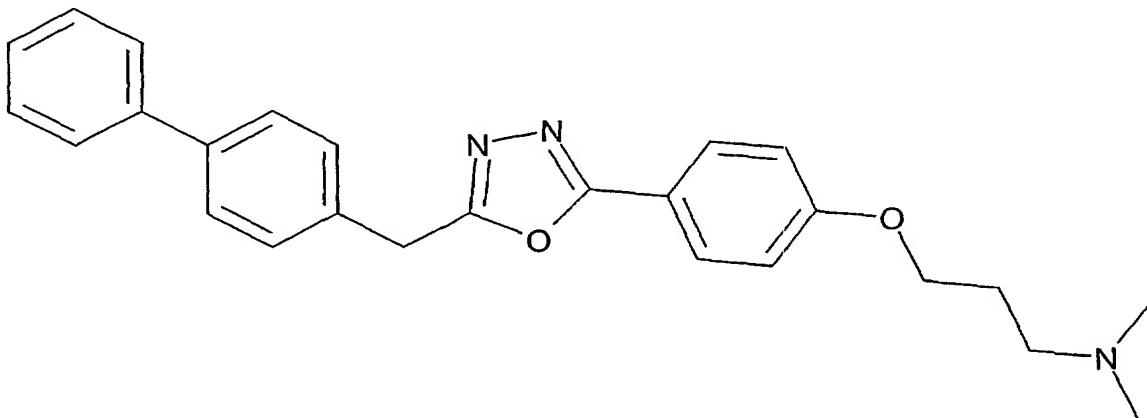
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 49e, from 4-Hydroxy-benzoic acid N'-(2-biphenyl-4-yl-acetyl)-hydrazide (1.56 g, 4.5 mM), triphenylphosphine (2.38 g, 9.0 mM), and triethylamine (2.26

-442-

mL, 16.2 mM) to afford 0.798g (54%) of 4-(5-Biphenyl-4-yl-methyl-[1,3,4]oxadiazol-2-yl)-phenol as a light yellow solid (MP 252-255 °C, MW 328.37).

¹H NMR (DMSO-d₆) δ 10.24 (s, 1H), 7.76 (d, 2H, J=9 Hz), 7.63 (m, 4H), 7.43 (m, 4H), 7.33 (t, 1H, J=7 Hz), 6.90 (d, 2H, J=9 Hz), and 4.34 (s, 2H). IR (KBr, cm⁻¹) 3055, 5 1612, 1569, 1497, 1431, 1370, 1285, 1238, 1173, 1087, 1030, 862, 819, 757, 692, and 522. MS (ESI) m/e 329, 327. Anal. Calcd for C₂₁H₁₆N₂O₂: C, 76.81; H, 4.91; N, 8.53. Found C, 76.41; H, 5.03; N, 8.19.

c) {3-[4-(5-Biphenyl-4-yl-methyl-[1,3,4]oxadiazol-2-yl)-phenoxy]-propyl}-dimethyl-
10 amine

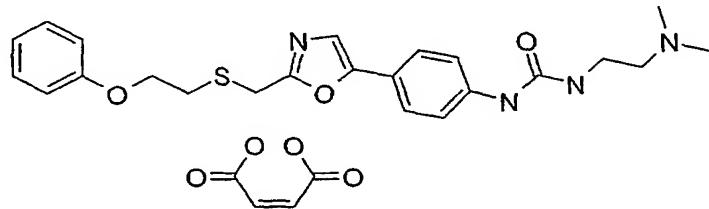


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 50f, from 4-(5-Biphenyl-4-yl-methyl-[1,3,4]oxadiazol-2-yl)-phenol (0.328 g, 1.0 mM), 3-chloro-N,N-dimethylpropylamine hydrochloride (0.174 g, 1.1 mM), and sodium hydride (0.092 g, 2.3 mM) in 7 mL DMF to afford 0.461 g of a brown gum. A second lot of the above compound was prepared in a manner similar to that exemplified for the preparation of Example 50f, from 4-(5-Biphenyl-4-yl-methyl-[1,3,4]oxadiazol-2-yl)-phenol (0.164 g, 0.5 mM), 3-chloro-N,N-dimethylpropylamine hydrochloride (0.087 g, 0.55 mM), and cesium carbonate (0.197 g, 0.6 mM) in 3 mL
15 DMF to afford 0.173 g of a yellow-orange solid. The combined lots were purified by Chromatotron radial chromatography on silica gel (isocratic elution with 97:3 Et₂O/2.0 M ammonia in methanol) to afford 0.113 g (18%) of {3-[4-(5-Biphenyl-4-yl-methyl-[1,3,4]oxadiazol-2-yl)-phenoxy]-propyl}-dimethyl-amine as a white solid (MP 95-97 °C, MW 413.52).

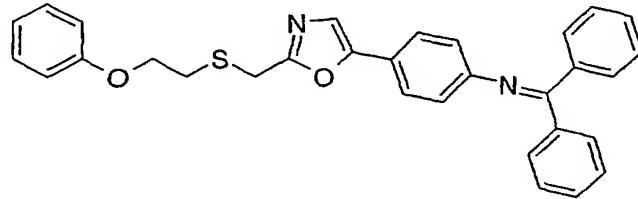
¹H NMR (CDCl₃) δ 7.94 (d, 2H, J=9 Hz), 7.58 (d, 2H, J=8 Hz), 7.57 (d, 2H, J=7 Hz), 7.44 (t, 2H, J=8 Hz), 7.43 (d, 2H, J=8 Hz), 7.34 (t, 1H, J=7 Hz), 6.96 (d, 2H, J=9 Hz), 4.31 (s, 2H), 4.12 (t, 2H, J=6 Hz), 2.81 (m, 2H), 2.53 (bs, 6H), and 2.20 (m, 2H). IR (KBr, cm⁻¹) 2943, 2857, 2813, 2762, 1613, 1568, 1501, 1473, 1249, 1174, 1035, 832, 5 757, 739, and 699. MS (ESI) m/e 414, 412. Anal. Calcd for C₂₆H₂₇N₃O₂: C, 75.52; H, 6.58; N, 10.16. Found C, 75.12; H, 6.54; N, 10.01. Analytical HPLC: 100% purity.

Example 250

Preparation of 1-(2-Dimethylamino-ethyl)-3-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-10 oxazol-5-yl]-phenyl}-urea maleate



a) Benzhydrylidene-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenyl}-amine

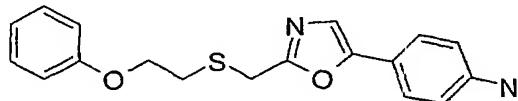


15 Combined 5-(4-bromo-phenyl)-2-(2-phenoxy-ethylsulfanylmethyl)-oxazole (0.5 g, 1.28 mmol, 1 eq., Example 268f), benzophenone imine (0.30 g, 1.54 mmol, 1.2 eq.), tris(dibenzylideneacetone)dipalladium(0) (3 mg, 3.2 μmol, 0.25%), (±)-BINAP (6 mg, 9.6 μmol, 0.75%), and sodium tert-butoxide (0.17 g, 1.79 mmol, 1.4 eq.) in toluene (10 mL) and heated to 105°C overnight. Diluted the cooled reaction with EtOAc and washed with water. The organic layer was collected, dried over MgSO₄, filtered, and the solvent removed leaving an orange oil which was purified via normal phase chromatography using 25% EtOAc in hexanes as the mobile phase leaving benzhydrylidene-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenyl}-amine (0.63 g, 100% yield) as a yellow oil.

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¹H NMR (DMSO-d₆) δ 7.67 (m, 2H), 7.48 (m, 7H), 7.25 (m, 6H), 6.93 (m, 3H), 6.77 (m, 2H), 4.16 (t, 2H, J=7 Hz), 4.01 (s, 2H), 2.98 (t, 2H, J=7 Hz). IR (CHCl₃, cm⁻¹) 3003.6, 1600.7, 1570.8, 1494.6, 1293.1, 1241. MS(ES⁺) m/e 491 [M+H]⁺. Anal. Calcd. for C₃₁H₂₆N₂O₂S C, 75.89; H, 5.34; N, 5.71. Found C, 75.50; H, 5.42; N, 5.63. M.P.= 5 86-90°C.

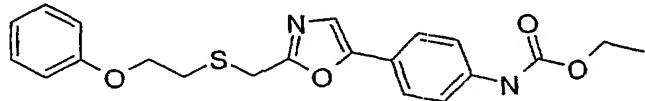
b) 4-[2-(2-Phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenylamine



A THF solution (15 mL) of benzhydrylidene-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenyl}-amine (2.0 g, 4.08 mmol, 1 eq.) was treated with 0.75 mL of 2 M aqueous HCl and the solution allowed to stir at room temperature for 1 hour. Diluted with 0.5 M aqueous HCl and extracted with EtOAc. Collected the organic layer, dried over MgSO₄, filtered, and removed the solvent in vacuo leaving an orange oil which was purified via normal phase chromatography using a step gradient of 10 EtOAc in hexanes as the mobile phase resulting in 4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenylamine (1.2 g, 90% yield) as yellow solid after removal of the solvent. 15

¹H NMR (DMSO-d₆) δ 7.27 (m, 4H), 6.93 (m, 3H), 6.60 (m, 2H), 4.16 (t, 2H, J=7 Hz), 4.0 (s, 2H), 2.98 (t, 2H, J=7 Hz). IR (KBr, cm⁻¹) 3461.7, 3339, 1627.5, 1613.9, 1601, 1505.7, 1488.7, 1299, 1242, 1231.3, 1175, 1099.3, 828.1, 757.8, 749.9. MS(ES⁺) 20 m/e 327 [M+H]⁺. Anal. Calcd. for C₁₈H₁₈N₂O₂S C, 66.23; H, 5.56; N, 8.58. Found C, 65.98; H, 5.56; N, 8.45. M.P.=110-111°C.

c) {4-[2-(2-Phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenyl}-carbamic acid ethyl ester



25

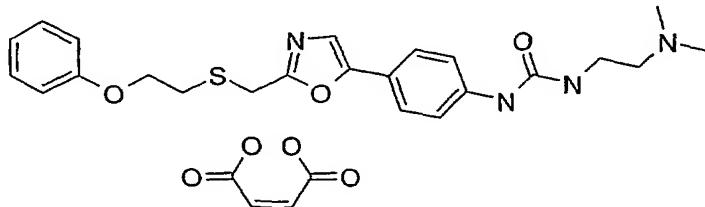
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 101a from 4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenylamine (1.63 g, 4.99 mmol, 1 eq.) and ethyl chloroformate (0.81 g, 7.49 mmol, 1.5

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eq.) to produce {4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenyl}-carbamic acid ethyl ester (1.99 g, 100% yield) as a yellow solid.

¹H NMR (DMSO-d₆) δ 9.81 (s, 1H), 7.57 (m, 4H), 7.47 (s, 1H), 7.27 (m, 2H), 6.93 (m, 3H), 4.15 (m, 4H), 4.04 (s, 2H), 3.0 (t, 2H, J=7 Hz), 1.25 (t, 3H, J=7 Hz).
5 MS(ES⁺) m/e 399 [M+H]⁺. MS(ES⁻) m/e 397 [M-H]⁻.

d) Preparation of 1-(2-dimethylamino-ethyl)-3-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenyl}-urea maleate



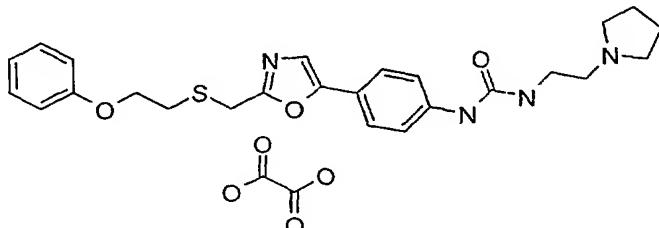
10 The above compound was prepared in a manner similar to that exemplified for the preparation of Example 101e from {4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenyl}-carbamic acid ethyl ester (1.0 g, 2.5 mmol, 1 eq.) and N,N-dimethylethylenediamine (0.26 g, 3.0 mmol, 1.2 eq.) to produce 1-(2-dimethylamino-ethyl)-3-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenyl}-urea (1.05 g, 95% yield) as a yellow oil.
15

20 An EtOAc solution of 1-(2-dimethylamino-ethyl)-3-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenyl}-urea (0.51 g, 1.16 mmol, 1 eq.) was treated dropwise with an EtOAc solution of maleic acid (0.15 g, 1.28 mmol, 1.1 eq.). Removed the EtOAc in vacuo and added Et₂O and boiled the resulting gum until 1-(2-dimethylamino-ethyl)-3-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenyl}-urea maleate (0.43 g, 68% yield) was obtained as a yellow solid.

25 ¹H NMR (DMSO-d₆) δ 8.98 (s, 1H), 7.54 (m, 4H), 7.44 (s, 1H), 7.27 (m, 2H), 6.93 (m, 3H), 6.41 (t, 1H, J=6 Hz), 6.03 (s, 2H), 4.17 (t, 2H, J=7 Hz), 4.04 (s, 2H), 3.44 (m, 2H), 3.15 (m, 2H), 2.99 (t, 2H, J=7 Hz), 2.82 (s, 6H). IR (KBr, cm⁻¹) 3402.4, 1695.6, 1607.6, 1547.2, 1498.6, 1465, 1359.6, 1322.2, 1227.1, 867.3, 754.4. MS(ES⁺) m/e 441 [M+H]⁺. MS(ES⁻) m/e 439 [M-H]⁻. Anal. Calcd. for C₂₇H₃₂N₄O₇S C, 58.26; H, 5.79; N, 10.07. Found C, 57.68; H, 5.58; N, 9.88. Analytical LC/MS 100% (diode array detector). M.P.=105-107°C.

Example 251

Preparation of 1-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenyl}-3-pyrrolidin-1-ylmethyl-urea oxalate



5

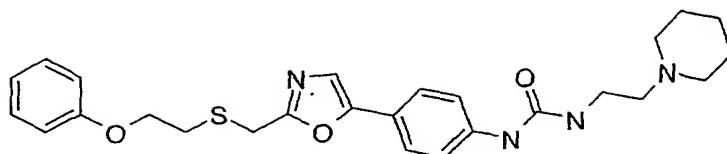
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 101e from {4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenyl}-carbamic acid ethyl ester (1.0 g, 2.5 mmol, 1 eq.) and 1-(2-aminoethyl)pyrrolidine (0.34 g, 3.0 mmol, 1.2 eq.) to produce 1-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenyl}-3-pyrrolidin-1-ylmethyl-urea (1.14 g, 97% yield) as a yellow oil.

An EtOAc solution of the urea was treated with an EtOAc solution of oxalic acid (0.20 g, 1.1 eq.) producing 1-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenyl}-3-pyrrolidin-1-ylmethyl-urea oxalate (0.57 g) as an off-white solid that was collected by filtration.

¹H NMR (DMSO-d₆) δ 9.37 (s, 1H), 7.53 (bs, 4H), 7.43 (s, 1H), 7.27 (m, 2H), 7.09 (bs, 1H), 6.93 (m, 3H), 4.17 (t, 2H, J=7 Hz), 4.04 (s, 2H), 3.41 (bs, 2H), 3.22 (m, 6H), 2.99 (t, 2H, J=7 Hz), 1.92 (bs, 4H). IR (KBr, cm⁻¹) 3367.2, 3283.3, 1733.7, 1688.4, 1587.2, 1536, 1504.2, 1317.2, 1233.3, 711.6. MS(ES⁺) m/e 467 [M+H]⁺. MS(ES⁻) m/e 465 [M-H]⁻. Anal. Calcd. for C₂₇H₃₂N₄O₇S C, 58.26; H, 5.79; N, 10.07. Found C, 57.82; H, 5.76; N, 9.86. Analytical LC/MS 95% purity (diode array detector). M.P.=124-126°C.

Example 252

Preparation of 1-{4-[2-(2-Phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenyl}-3-piperidin-1-ylmethyl-urea

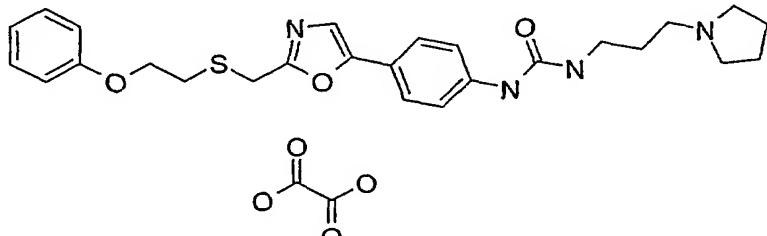


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 101e from {4-[2-(2-phenoxyethylsulfanyl)methyl]-oxazol-5-yl}-phenyl}-carbamic acid ethyl ester (1.75 g, 4.39 mmol, 1 eq.) and 1-(2-aminoethyl)piperidine (0.68 g, 5.27 mmol, 1.2 eq.) to obtain 1-{4-[2-(2-phenoxyethylsulfanyl)methyl]-oxazol-5-yl}-phenyl}-3-piperidin-1-ylmethyl-urea (0.88 g, 42% yield) as a yellow solid.

¹H NMR (DMSO-d₆) δ 8.85 (s, 1H), 7.50 (m, 5H), 7.27 (m, 2H), 6.92 (m, 3H), 6.10 (t, 1H, J=6 Hz), 4.17 (t, 2H, J=7 Hz), 4.03 (s, 2H), 3.19 (m, 2H), 2.99 (t, 2H, J=7 Hz), 2.34 (m, 6H), 1.51 (m, 4H), 1.38 (m, 2H). IR (CHCl₃, cm⁻¹) 2941.6, 1684.5, 1601, 1587.4, 1520.3, 1504.9, 1498.4, 1243.7. MS(ES⁺) m/e 481 [M+H]⁺. MS(ES⁻) m/e 479 [M-H]⁻. Analytical LC/MS 100% purity (diode array detector). M.P.=84-87°C.

Example 253

Preparation of 1-{4-[2-(2-Phenoxyethylsulfanyl)methyl]-oxazol-5-yl}-phenyl}-3-(3-pyrrolidin-1-yl-propyl)-urea oxalate



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 101e from {4-[2-(2-phenoxyethylsulfanyl)methyl]-oxazol-5-yl}-phenyl}-carbamic acid ethyl ester (0.55 g, 1.38 mmol, 1 eq.) and 1-(3-aminopropyl)pyrrolidine (0.21 g, 1.66 mmol, 1.2 eq.) to produce 1-{4-[2-(2-phenoxyethylsulfanyl)methyl]-oxazol-5-yl}-phenyl}-3-(3-pyrrolidin-1-yl-propyl)-urea (0.42 g, 64% yield) as a yellow oil.

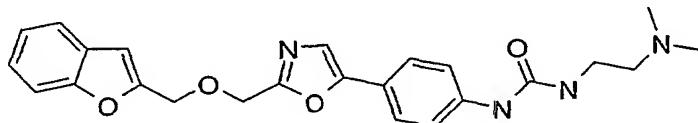
An EtOAc solution of the free base was treated with an EtOAc solution of oxalic acid (0.09 g, 1.1 eq.) producing 1-{4-[2-(2-phenoxy-ethylsulfanyl methyl)-oxazol-5-yl]-phenyl}-3-(3-pyrrolidin-1-yl-propyl)-urea oxalate (0.46 g) as a light yellow solid.

¹H NMR (DMSO-d₆) δ 9.25 (s, 1H), 7.53 (bs, 4H), 7.42 (s, 1H), 7.27 (m, 2H), 5 6.93 (m, 4H), 4.17 (t, 2H, J=7 Hz), 4.04 (s, 2H), 3.24 (b, 4H), 3.16 (m, 4H), 2.99 (t, 2H, J=7 Hz), 1.92 (bs, 4H), 1.81 (m, 2H). IR (KBr, cm⁻¹) 3383, 3039.7, 1688.7, 1586.4, 1535.5, 1504.4, 1413.8, 1317.3, 1236.1, 840, 756.6, 694.7. MS(ES⁺) m/e 481 [M+H]⁺. MS(ES⁻) m/e 479 [M-H]⁻. Analytical LC/MS 85% purity (diode array detector).

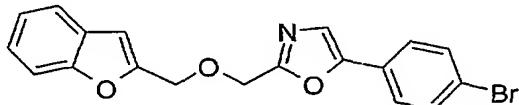
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Example 254

Preparation of 1-{4-[2-(benzofuran-2-ylmethoxymethyl)-oxazol-5-yl]-phenyl}-3-(2-dimethylamino-ethyl)-urea



a) 2-(Benzofuran-2-ylmethoxymethyl)-5-(4-bromo-phenyl)-oxazole



15

A THF solution of 1-benzofuran-2-ylmethanol (2.2 g, 14.85 mmol, 1 eq.) was treated with NaH (0.65 g, 60% in oil, 16.34 mmol, 1.1 eq.) and stirred at room temperature for 5 minutes before 5-(4-bromo-phenyl)-2-chloromethyl-oxazole (4.05 g, 14.85 mmol, 1 eq.) was added as a solid. The reaction was allowed to stir overnight at room temperature. The solvent was removed in vacuo and the oil dissolved in EtOAc and washed with water and brine. The organic layer was collected, dried over MgSO₄, filtered, and the solvent removed leaving a brown oil that was purified by normal phase chromatography using a step gradient of EtOAc in hexanes as the mobile phase. Removal of the solvent and recrystallization from Et₂O/hexanes left 2-(benzofuran-2-ylmethoxymethyl)-5-(4-bromo-phenyl)-oxazole (3.82 g, 67% yield) as a yellow solid.

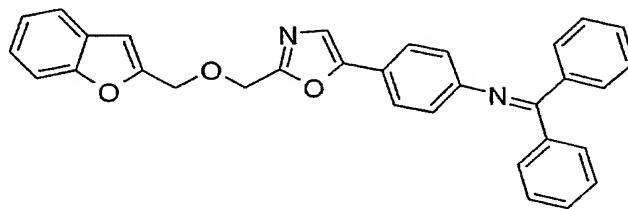
¹H NMR (DMSO-d₆) δ 7.74 (s, 1H), 7.65 (m, 5H), 7.55 (m, 1H), 7.27 (m, 2H), 6.95 (s, 1H), 4.76 (s, 2H), 4.71 (s, 2H). IR (KBr, cm⁻¹) 3096.5, 1480.8, 1405, 1067.7,



1009.9, 940.5, 821.4, 759.5, 503.6. MS(FAB⁺) m/e 384, 386 [M+H]⁺. Analytical LC/MS 100% purity (diode array detector). M.P.=80-82°C.

- b) Benzhydrylidene-{4-[2-(benzofuran-2-ylmethoxymethyl)-oxazol-5-yl]-phenyl}-amine

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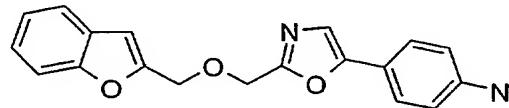


The above compound was prepared in a manner similar to that exemplified in example 250a from 2-(benzofuran-2-ylmethoxymethyl)-5-(4-bromo-phenyl)-oxazole (4.0 g, 10.41 mmol, 1 eq.), benzophenone imine (2.26 g, 12.49 mmol, 1.2 eq.), and sodium 10 tert-butoxide (1.40 g, 14.57 mmol, 1.4 eq.) to produce benzhydrylidene-{4-[2-(benzofuran-2-ylmethoxymethyl)-oxazol-5-yl]-phenyl}-amine (4.72 g, 94% yield) as a yellow foam.

15 ¹H NMR (DMSO-d6) δ 7.64 (m, 3H), 7.51 (m, 7H), 7.26 (m, 7H), 6.95 (s, 1H), 6.77 (m, 2H), 4.73 (s, 2H), 4.66 (s, 2H). MS(ES⁺) m/e 485 [M+H]⁺.

c)

- 4-[2-(Benzofuran-2-ylmethoxymethyl)-oxazol-5-yl]-phenylamine



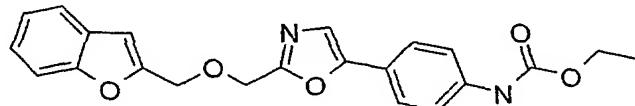
The above compound was prepared in a manner similar to that exemplified in Example 250b from benzhydrylidene-{4-[2-(benzofuran-2-ylmethoxymethyl)-oxazol-5-yl]-phenyl}-amine (4.6 g, 9.49 mmol, 1 eq.) and 2M aqueous HCl (1.5 mL) to produce 4-[2-(benzofuran-2-ylmethoxymethyl)-oxazol-5-yl]-phenylamine (2.78 g, 91% yield) as a yellow solid.

20 ¹H NMR (DMSO-d6) δ 7.63 (m, 1H), 7.56 (m, 1H), 7.28 (m, 5H), 6.95 (s, 1H), 6.61 (m, 2H), 5.46 (s, 2H), 4.73 (s, 2H), 4.64 (s, 2H). IR (KBr, cm⁻¹) 3322, 3222.3, 2909.7, 1610, 1502.3, 1451.8, 1437.7, 1363.7, 1281.9, 1236.9, 1129.5, 1077.6, 943.7, 808.1, 755.2, 687.4, 520.2. MS(ES⁺) m/e 321 [M+H]⁺, 131. Anal. Calcd. for

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$C_{19}H_{16}N_2O_3$ C, 71.24; H, 5.03; N, 8.74. Found C, 71.07; H, 5.03; N, 8.72. Analytical LC/MS 100% purity (diode array detector). M.P.=96-98°C.

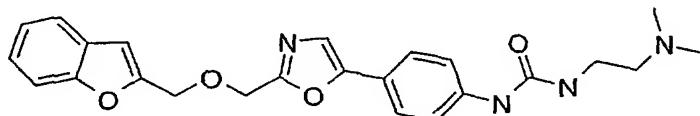
- d) {4-[2-(Benzofuran-2-ylmethoxymethyl)-oxazol-5-yl]-phenyl}-carbamic acid ethyl ester



This above compound was prepared in a manner similar to that exemplified in Example 101a from 4-[2-(benzofuran-2-ylmethoxymethyl)-oxazol-5-yl]-phenylamine (2.54 g, 7.93 mmol, 1 eq.) and ethyl chloroformate (1.29 g, 11.9 mmol, 1.5 eq.) to produce {4-[2-(benzofuran-2-ylmethoxymethyl)-oxazol-5-yl]-phenyl}-carbamic acid ethyl ester (3.08 g, 99% yield) as a yellow solid.

1H NMR (DMSO-d₆) δ9.82 (s, 1H), 7.58 (m, 7H), 7.27 (m, 2H), 6.96 (s, 1H), 4.75 (s, 2H), 4.69 (s, 2H), 4.14 (q, 2H, J=7 Hz), 1.25 (t, 3H, J=7 Hz). IR (CHCl₃, cm⁻¹) 3434, 3010.7, 1733, 1600.3, 1586.6, 1521.5, 1453.9, 1416.2, 1316.6, 1255.1, 1224.7, 1205.9, 1135, 1069.2, 943.6, 838.8, 818.4. MS(ES⁺) m/e 393 [M+H]⁺, 131. MS(ES⁻) m/e 391 [M-H]⁻, 131. Anal. Calcd. for $C_{22}H_{20}N_2O_5$ C, 67.34; H, 5.14; N, 7.14. Found C, 67.65; H, 5.08; N, 7.10. Analytical LC/MS 100% purity (diode array detector).

- e) Preparation of 1-{4-[2-(benzofuran-2-ylmethoxymethyl)-oxazol-5-yl]-phenyl}-3-(2-dimethylamino-ethyl)-urea

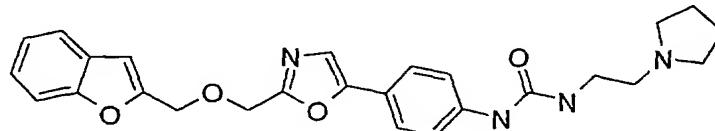


The above compound was prepared in a manner similar to that exemplified in Example 101e from {4-[2-(benzofuran-2-ylmethoxymethyl)-oxazol-5-yl]-phenyl}-carbamic acid ethyl ester (1.0 g, 2.55 mmol, 1 eq.) and N,N-dimethylethylenediamine (0.27 g, 3.06 mmol, 1.2 eq.) to produce 1-{4-[2-(benzofuran-2-ylmethoxymethyl)-oxazol-5-yl]-phenyl}-3-(2-dimethylamino-ethyl)-urea (0.72 g, 65% yield) as an off-white solid when triturated with hot EtOAc and cooled.

¹H NMR (DMSO-d₆) δ 8.83 (s, 1H), 7.63 (m, 1H), 7.5 (m, 6H), 7.27 (2H), 6.96 (s, 1H), 6.14 (t, 1H, J=6 Hz), 4.75 (s, 2H), 4.68 (s, 2H), 3.18 (m, 2H), 2.32 (t, 2H, J=7 Hz), 2.17 (s, 6H). IR (KBr, cm⁻¹) 3311.1, 2938.4, 2902.9, 2860.3, 2819.1, 1631.2, 1585.8, 1504.6, 1455.8, 1417.7, 1310.7, 1256.1, 1131.2, 1074, 989.8, 943.2, 839.1, 805.3, 5 749.9. MS(ES⁺) m/e 435 [M+H]⁺. MS(ES⁻) m/e 433 [M-H]⁻. Anal. Calcd. for C₂₄H₂₆N₄O₄ C, 66.34; H, 6.03; N, 12.89. Found C, 66.55; H, 5.99; N, 12.68. Analytical LC/MS 100% purity (diode array detector). M.P.=150-154°C.

Example 255

- 10 Preparation of 1-{4-[2-(Benzofuran-2-ylmethoxymethyl)-oxazol-5-yl]-phenyl}-3-(2-pyrrolidin-1-yl-ethyl)-urea

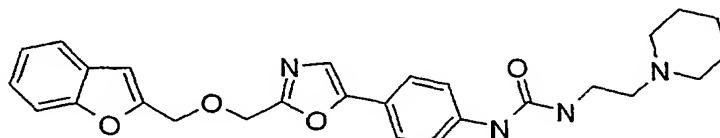


The above compound was prepared in a manner similar to that exemplified in Example 101e from {4-[2-(benzofuran-2-ylmethoxymethyl)-oxazol-5-yl]-phenyl}-carbamic acid ethyl ester (1.0 g, 2.55 mmol, 1 eq.) and N-(2-aminoethyl)pyrrolidine (0.35 g, 3.06 mmol, 1.2 eq.) to produce 1-{4-[2-(benzofuran-2-ylmethoxymethyl)-oxazol-5-yl]-phenyl}-3-(2-pyrrolidin-1-yl-ethyl)-urea (0.86 g, 73% yield) as a white solid.

15 ¹H NMR (DMSO-d₆) δ 8.84 (s, 1H), 7.63 (m, 1H), 7.5 (m, 6H), 7.27 (m, 2H), 6.96 (s, 1H), 6.17 (t, 1H, J=6 Hz), 4.75 (s, 2H), 4.68 (s, 2H), 3.2 (m, 2H), 2.46 (m, 6H), 20 1.70 (bs, 4H). IR (KBr, cm⁻¹) 3346, 2962.2, 2798.2, 1649.4, 1558.4, 1525.5, 1453.9, 1413.1, 1313.4, 1242.1, 1079.8, 754.1. MS(ES⁺) m/e 461 [M+H]⁺. MS(ES⁻) m/e 459 [M-H]⁻. Analytical LC/MS 100% purity (diode array detector). M.P.=124-126°C.

Example 256

- 25 Preparation of 1-{4-[2-(benzofuran-2-ylmethoxymethyl)-oxazol-5-yl]-phenyl}-3-(2-piperidin-1-yl-ethyl)-urea



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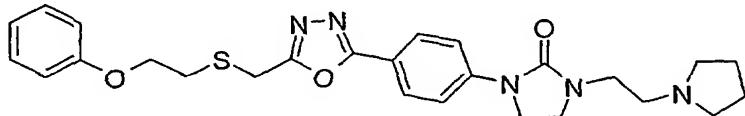
The above compound was prepared in a manner similar to that exemplified in Example 101e from {4-[2-(benzofuran-2-ylmethoxymethyl)-oxazol-5-yl]-phenyl}-carbamic acid ethyl ester (1.0 g, 2.55 mmol, 1 eq.) and N-(2-aminoethyl)piperidine (0.39 g, 3.06 mmol, 1.2 eq.) to produce 1-{4-[2-(benzofuran-2-ylmethoxymethyl)-oxazol-5-yl]-phenyl}-3-(2-piperidin-1-yl-ethyl)-urea (0.60 g, 50% yield) as a light yellow solid on trituration with Et₂O.

¹H NMR (DMSO-d6) δ 8.86 (s, 1H), 7.63 (m, 1H), 7.5 (m, 6H), 7.27 (m, 2H), 6.96 (s, 1H), 6.1 (t, 1H, J=6 Hz), 4.75 (s, 2H), 4.68 (s, 2H), 3.19 (m, 2H), 2.34 (m, 6H), 1.51 (m, 4H), 1.39 (m, 2H). IR (KBr, cm⁻¹) 3323.1, 2923.8, 2856, 2786.8, 1656.3, 1554.3, 1452.8, 1410.3, 1309.8, 1232.5, 1136.1, 1069.6, 941.7, 839.6, 742.2. MS(ES⁺) 475 [M+H]⁺. MS(ES⁻) 473 [M-H]⁻. Anal. Calcd. for C₂₇H₃₀N₄O₄ C, 68.34; H, 6.37; N, 11.81. Found C, 68.05; H, 6.12; N, 11.69. Analytical LC/MS 100% purity (diode array detector). M.P.=102-104°C.

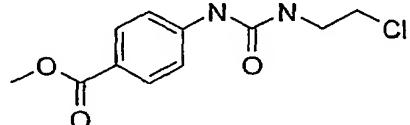
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Example 257

Preparation of 1-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-3-(2-pyrrolidin-1-yl-ethyl)-imidazolidin-2-one



a) 4-[3-(2-Chloro-ethyl)-ureido]-benzoic acid methyl ester



20

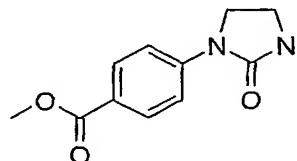
A THF solution of methyl 4-aminobenzoate (14.05 g, 92.91 mmol, 1 eq.) was treated with 2-chloroethyl isocyanate (10 g, 94.77 mmol, 1.02 eq.) and stirred overnight at room temperature. Removed the solvent and recrystallized the orange solid from EtOAc leaving 4-[3-(2-chloro-ethyl)-ureido]-benzoic acid methyl ester (16.41 g, 69% yield) as a yellow solid.

¹H NMR (DMSO-d6) δ 9.08 (s, 1H), 7.84 (d, 2H, J=9 Hz), 7.52 (d, 2H, J=9 Hz), 6.55 (t, 1H, J=6 Hz), 3.8 (s, 3H), 3.67 (t, 2H, J=7 Hz), 3.44 (m, 2H). IR (KBr, cm⁻¹) 3339.2, 3288.1, 1714.6, 1639.2, 1596, 1565.3, 1438, 1282.8, 1243.6, 1170.3, 1108.2.

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MS(ES^+) m/e 257, 259 [$\text{M}+\text{H}]^+$. Analytical LC/MS 100% purity (light scattering).
M.P.=163-165°C.

b) 4-(2-Oxo-imidazolidin-1-yl)-benzoic acid methyl ester

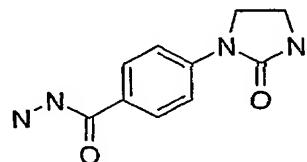


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A suspension of NaH (5.24 g, 60% in oil, 130.89 mmol, 2.1 eq.) in THF was treated dropwise with a THF solution of 4-[3-(2-chloro-ethyl)-ureido]-benzoic acid methyl ester (16 g, 62.33 mmol, 1 eq.) and stirred for 1 hour at room temperature and then 1 hour at reflux. The solvent was removed in vacuo and the residue dissolved in CH_2Cl_2 and washed with water. The organic layer was collected, dried over MgSO_4 , and the solvent removed leaving a tan solid which was recrystallized from EtOAc/MeOH to produce 4-(2-oxo-imidazolidin-1-yl)-benzoic acid methyl ester (8.22 g, 60% yield) as an off-white solid.

¹H NMR (DMSO-d6) δ 7.9 (d, 2H, J=9 Hz), 7.69 (d, 2H, J=9 Hz), 7.23 (s, 1H), 3.9 (m, 2H), 3.81 (s, 3H), 3.43 (t, 2H, J=8 Hz). IR (KBr, cm^{-1}) 3241.8, 3100.1, 1721.5, 1680.8, 1431.8, 1284.6, 1264.4, 1182.2, 1109.9, 853.4. MS(ES^+) m/e 221 [$\text{M}+\text{H}]^+$. Anal. Calcd. for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_3$ C, 59.99; H, 5.49; N, 12.72. Found C, 60.16; H, 5.38; N, 12.64. Analytical LC/MS 100% purity (diode array and light scattering detection). M.P.>200°C.

20 c) 4-(2-Oxo-imidazolidin-1-yl)-benzoic acid hydrazide



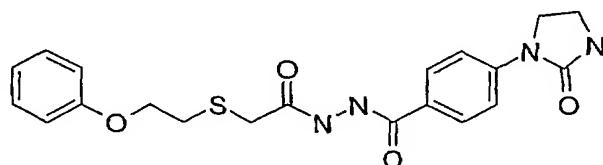
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 101b from 4-(2-oxo-imidazolidin-1-yl)-benzoic acid methyl ester (8.18 g, 37.14 mmol, 1 eq.) and hydrazine (11.90 g, 371.4 mmol, 10 eq.) except that MeOH and THF were used as solvents to produce 4-(2-oxo-imidazolidin-1-yl)-benzoic acid hydrazide (3.36 g, 41% yield) as an off-white solid.

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¹H NMR (DMSO-d₆) δ 9.61 (s, 1H), 7.79 (d, 2H, J=9 Hz), 7.6 (d, 2H, J=9 Hz), 7.1 (s, 1H), 4.41 (s, 2H), 3.87 (t, 2H, J=8 Hz), 3.41 (t, 2H, J=8 Hz). IR (KBr, cm⁻¹) 3298.7, 3213.8, 3198.1, 1700.3, 1635.3, 1606, 1487.2, 1443.8, 1429.2, 1407.1, 1311.1, 1261.5, 940.1, 843.7, 745.4. MS(ES⁺) m/e 221 [M+H]⁺. M.P.>200°C.

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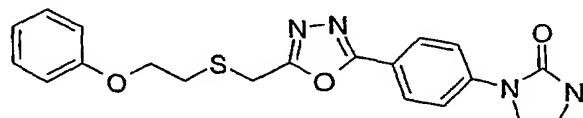
- d) 4-(2-Oxo-imidazolidin-1-yl)-benzoic acid N'-[2-(2-phenoxy-ethylsulfanyl)-acetyl]-hydrazide



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 101c from 4-(2-oxo-imidazolidin-1-yl)-benzoic acid hydrazide (2.0 g, 9.08 mmol, 1 eq.) and (2-phenoxyethylthio)acetic acid (1.93 g, 9.08 mmol, 1 eq.) to produce 4-(2-oxo-imidazolidin-1-yl)-benzoic acid N'-(2-(2-phenoxy-ethylsulfanyl)-acetyl)-hydrazide (2.79 g, 74% yield) as a tan solid.

¹H NMR (DMSO-d₆) δ 10.3 (s, 1H), 10 (s, 1H), 7.86 (d, 2H, J=9 Hz), 7.66 (d, 2H, J=9 Hz), 7.29 (m, 2H), 7.16 (s, 1H), 6.95 (m, 3H), 4.2 (t, 2H, J=7 Hz), 3.9 (m, 2H), 3.43 (m, 4H), 3.05 (m, 2H). IR (KBr, cm⁻¹) 3300.6, 1696.1, 1656.6, 1611.3, 1484, 1241, 1032.7, 745.4. MS(ES⁺) m/e 415 [M+H]⁺. Anal. Calcd. for C₂₀H₂₂N₄O₄S C, 57.96; H, 5.35; N, 13.52. Found C, 57.57; H, 5.4; N, 13.41.

e) 1-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-imidazolidin-2-one

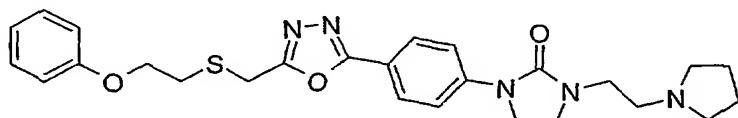


The above compound was prepared in a similar manner to that exemplified for the preparation of Example 101d from 4-(2-oxo-imidazolidin-1-yl)-benzoic acid N'-(2-(2-phenoxy-ethylsulfanyl)-acetyl)-hydrazide (2.6 g, 6.27 mmol, 1 eq.) to produce 1-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-imidazolidin-2-one (1.02 g, 41% yield) as a brown solid.

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¹H NMR (DMSO-d₆) δ 7.89 (d, 2H, J=9 Hz), 7.77 (d, 2H, J=9 Hz), 7.25 (m, 3H), 6.93 (m, 3H), 4.2 (m, 4H), 3.92 (m, 2H), 3.44 (m, 2H), 3.0 (t, 2H, J=7 Hz). IR (KBr, cm⁻¹) 3265, 1707.8, 1585.2, 1505, 1496.2, 1487.2, 1408.7, 1268.1, 1233.5, 845.65, 754. MS(ES⁺) m/e 397 [M+H]⁺. MS(ES-) m/e 395 [M-H]⁻. Anal. Calcd. for C₂₀H₂₀N₄O₃S C, 60.59; H, 5.08; N, 14.13. Found C, 60.23; H, 5.08; N, 13.66. Analytical LC/MS 100% purity (diode array detector). M.P.=108-181°C.

f) 1-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-3-(2-pyrrolidin-1-yl-ethyl)-imidazolidin-2-one



10

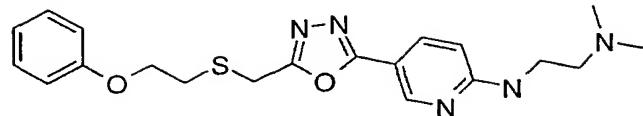
A DMF suspension of 1-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-imidazolidin-2-one (0.76 g, 1.92 mmol, 1 eq.) and 1-(chloroethyl)pyrrolidine hydrochloride (0.34 g, 2.02 mmol, 1.05 eq.) was treated with NaH (0.16 g, 60% in oil, 4.03 mmol, 2.1 eq.) and the reaction heated to 85°C overnight. The reaction was diluted with EtOAc and washed with water. The organic layer was collected, dried over MgSO₄, and the solvent removed leaving an orange/brown oil that was purified by normal phase chromatography using a step gradient of 2M NH₃ in MeOH in chloroform as the mobile phase leaving a yellow oil which produced 1-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-3-(2-pyrrolidin-1-yl-ethyl)-imidazolidin-2-one (0.28 g, 29% yield) as a yellow solid on trituration with ether.

¹H NMR (DMSO-d₆) δ 7.9 (d, 2H, J=9 Hz), 7.77 (d, 2H, J=9 Hz), 7.27 (m, 2H), 6.93 (m, 3H), 4.19 (m, 4H), 3.87 (m, 2H), 3.56 (m, 2H), 3.32 (m, 6H), 3.02 (t, 2H, J=7 Hz), 2.6 (bt, 2H), 1.68 (m, 4H). IR (KBr, cm⁻¹) 3403.8, 2948.7, 2922.6, 2769.3, 1688.4, 1613.2, 1507.1, 1485.9, 1424.2, 1268, 1242, 740.5. MS(ES⁺) m/e 494 [M+H]⁺.

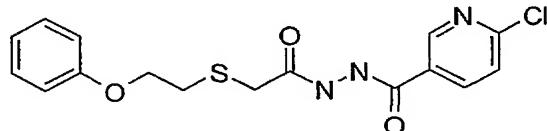
25 Analytical LC/MS 100% (diode array and light scattering detection). M.P.=125-129°C.

Example 258

Preparation of N,N-dimethyl-N'-{5-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-ethane-1,2-diamine



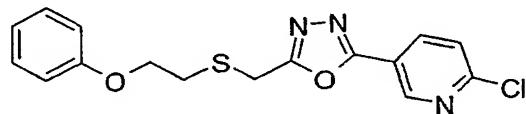
a) 6-Chloro-nicotinic acid N'-(2-(2-phenoxy-ethylsulfanyl)-acetyl)-hydrazide



The above compound was prepared in a similar manner to that exemplified for the preparation of Example 101c from 2-chloropyridine-5-carboxylic acid (Aldrich, 2.0 g, 12.69 mmol, 1 eq.), (2-phenoxy-ethylsulfanyl)-acetic acid hydrazide (Maybridge, 2.87 g, 12.69 mmol, 1 eq.), and EEDQ (3.45 g, 13.96 mmol, 1.1 eq.). The reaction was worked up as described and the brown oil purified by silica gel chromatography using a step gradient of EtOAc in hexanes as the mobile phase. Removal of the solvent in vacuo left 6-chloro-nicotinic acid N'-(2-(2-phenoxy-ethylsulfanyl)-acetyl)-hydrazide (3.95 g, 85% yield) as a white solid.

¹H NMR (DMSO-d6) δ 10.76 (s, 1H), 10.26 (s, 1H), 8.87 (m, 1H), 8.26 (m, 1H), 7.69 (d, 1H, J=8 Hz), 7.29 (m, 2H), 6.95 (m, 3H), 4.2 (t, 2H, J=7 Hz), 3.35 (s, 2H), 3.04 (t, 2H, J=7 Hz). IR (KBr, cm⁻¹) 3222.8, 1605.3, 1493, 1459.5, 1253.7, 1174.2, 1110.4, 1035.5, 756.3, 599.8. MS(ES⁺) m/e 366 [M+H]⁺, 272 [M-OPh]⁺. MS(ES⁻) m/e 364 [M-H]⁻. Analytical LC/MS 100% (diode array detection). M.P.=136-138°C.

b) 2-Chloro-5-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-pyridine

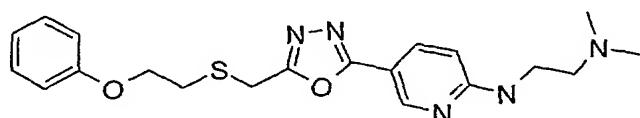


The above compound was prepared in a similar manner to that exemplified for the preparation of Example 101d from 6-chloro-nicotinic acid N'-(2-(2-phenoxy-ethylsulfanyl)-acetyl)-hydrazide (3.48 g, 9.51 mmol, 1 eq.). The crude material was purified by silica gel chromatography using a step gradient of EtOAc in hexanes as the mobile phase. The solvent was removed in vacuo leaving 2-chloro-5-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-pyridine (2.50 g, 76% yield) as an off-white solid.

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¹H NMR (DMSO-d₆) δ 8.97 (m, 1H), 8.36 (m, 1H), 7.75 (d, 1H, J=8 Hz), 7.26 (m, 2H), 6.92 (m, 3H), 4.25 (s, 2H), 4.19 (t, 2H, J=6 Hz), 3.04 (t, 2H, J=6 Hz). IR (KBr, cm⁻¹) 2924, 1602.7, 1570.5, 1499, 1465.5, 1385, 1248.7, 1176.5, 1136.6, 1114.2, 1035.7, 1004.6, 843.9, 750.5. MS(ES⁺) 346 [M-H]⁻. Analytical LC/MS 100% (diode array detection). M.P.=113-115°C.

c) N,N-Dimethyl-N'-{5-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-ethane-1,2-diamine



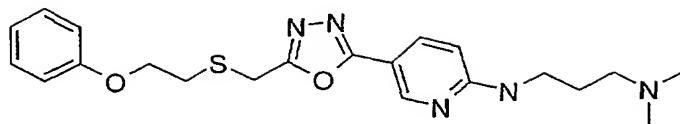
10 2-Chloro-5-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-pyridine (0.72 g, 2.07 mmol, 1 eq.) was suspended in N,N-dimethylethylenediamine (5 mL) and the reaction heated to 100°C for three hours. The reaction was diluted with EtOAc and washed two times with water and then brine. The organic layer was collected, dried over MgSO₄, filtered, and the solvent removed in vacuo leaving an orange oil that was purified by silica gel chromatography using 10% 2M NH₃ in MeOH in Et₂O as the mobile phase. Removal of the solvent in vacuo left an orange oil which was triturated with diethyl ether producing N,N-dimethyl-N'-{5-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-ethane-1,2-diamine (0.28 g, 34% yield) as an off-white solid.

20 ¹H NMR (DMSO-d₆) δ 8.54 (m, 1H), 7.82 (m, 1H), 7.27 (m, 3H), 6.93 (m, 3H), 6.64 (d, 1H, J=9 Hz), 4.17 (m, 4H), 3.41 (m, 2H), 3.01 (t, 2H, J=7 Hz), 2.42 (t, 2H, J=7 Hz), 2.18 (s, 6H). IR (CHCl₃, cm⁻¹) 3388.1, 3007.6, 2864.4, 2825.5, 2777.3, 1612.7, 1498.6, 1406.2, 1343.1, 1299.4, 1224.9, 1173.2, 1144.7, 1034.3, 957.4, 823.5. MS(ES⁺) m/e 400 [M+H]⁺. MS(ES⁻) m/e 398 [M-H]⁻. Analytical LC/MS 100% purity (diode array detection). M.P.=97-98°C.

Example 259

N,N-Dimethyl-N'-{5-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-propane-1,3-diamine

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The above compound was prepared in a similar manner to that exemplified for the preparation of Example 258 from 2-chloro-5-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-pyridine (0.75 g, 2.16 mmol, 1 eq.) and 3-dimethylaminopropylamine (6 mL). Purification and trituration as described left N,N-dimethyl-N'-(5-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl)-

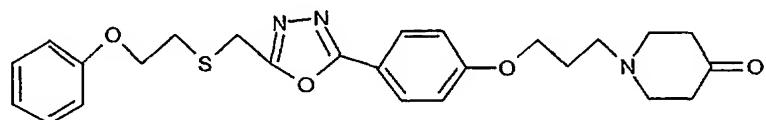
5 propane-1,3-diamine (0.31 g, 35% yield) as a white solid.

¹H NMR (DMSO-d₆) δ 8.54 (m, 1H), 7.82 (m, 1H), 7.39 (m, 1H), 7.27 (m, 2H), 6.93 (m, 3H), 6.58 (d, 1H, J=9 Hz), 4.17 (m, 4H), 3.33 (m, 2H), 3.01 (t, 2H, J=7 Hz), 2.27 10 (t, 2H, J=7 Hz), 2.13 (s, 6H), 1.67 (m, 2H). IR (CHCl₃, cm⁻¹) 3007.1, 2949.9, 2864.7, 2824.4, 1613.1, 1498.5, 1411.8, 1344.5, 1299, 1243.4, 1223.4, 1173.1, 1145.4, 1081.8, 1034.6. MS (ES⁺) m/e 414 [M+H]⁺. MS (ES⁻) m/e 412 [M-H]⁻. Anal. Calcd. for C₂₁H₂₇N₅O₂S C, 60.99; H, 6.58; N, 16.93. Found C, 60.94; H, 6.61; N, 16.60. Analytical LC/MS 100% purity (diode array detection). M.P.=94-96°C.

15

Example 260

Preparation of 1-(3-{4-[5-(2-Phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-piperidin-4-one



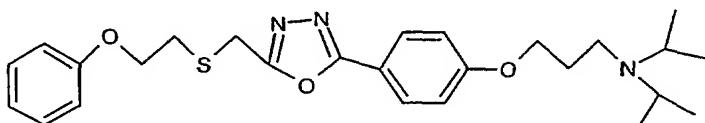
20 Prepared in a similar manner as 68b from 2-[4-(3-chloro-propoxy)-phenyl]-5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazole (0.350 g, 0.864 mM), piperidin-4-one, trifluoroacetic acid (0.921 g, 4.32 mM), NaI (0.065 g, 0.432 mM), and NaHCO₃ (0.399 g, 0.475 mM) in 3 mL DMF. The mixture was heated to 95° overnight in a sealed tube and worked up to give 0.304 g brown oil which was purified by column chromatography to 25 give 0.139 g of material which was combined with another lot and repurified on normal phase chromatography with 50:50 ethyl acetate:dichloromethane with 1% 2M ammonia in methanol to give 0.097 g (19%) of the title compound

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¹H NMR (DMSO-d₆) δ 7.9 (d, 2H, J=9 Hz), 7.2 (t, 2H, J=8 Hz), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 6H), 3.0 (t, 2H, J=6 Hz), 2.7 (m, 4H), 2.6 (t, 2H, J=7 Hz), 2.3 (m, 4H), 1.9 (m, 2H). IR (KBr, cm⁻¹) 2930, 1704, 1613, 1499, 1392, 1303, 1249, 1170, 1083, 1031, 847, 758, 694. MS (ESI) m/e 468.3, 500.3. Anal. Calcd for C₂₅H₂₉N₃O₄S₁: C, 64.22; H, 6.25; N, 8.98. Found C, 64.10; H, 6.27; N, 8.92. M.P.=55-57°C.

Example 261

Preparation of diisopropyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine



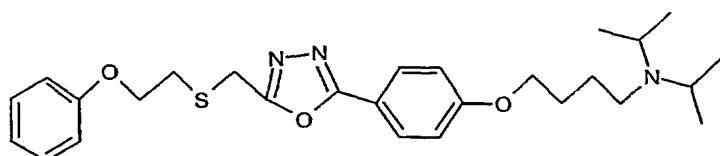
10

Prepared in a similar manner as 68b from 2-[4-(3-chloro-propoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole (0.477 g, 1.2 mM), diisopropylamine (8.66g. 86mM), NaI (0.088g, 0.59 mM), and NaHCO₃ (0.297 g, 3.54 mM) in 3 mL DMF. The solution was heated to 95° overnight in a sealed tube and worked up to give 0.417 g brown oil, which was purified by column chromatography as in 68b and recrystallized from ethyl ether and ethyl acetate to give 0.266 g (48%) of the title compound.

15 ¹H NMR (DMSO-d₆) δ 7.9 (d, 2H, J=9 Hz), 7.2 (t, 2H, J=8 Hz), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (m, 2H), 3.0 (m, 4H), 2.6 (m, 2H), 1.8 (m, 2H), 0.9 (m, 12H). IR (KBr, cm⁻¹) 2965, 1616, 1501, 1265, 1242, 1176, 751. MS (ESI) m/e 470. 20 Anal. Calcd for C₂₆H₃₅N₃O₃S₁: C, 66.49; H, 7.51; N, 8.95. Found C, 66.08; H, 7.57; N, 8.76. M.P.=30-33°C. HPLC 100%.

Example 262

Preparation of diisopropyl-(4-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-butyl)-amine



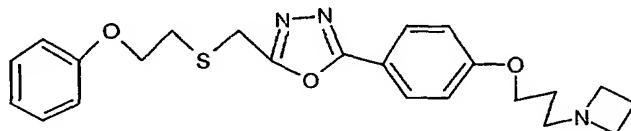
-460-

Prepared in a similar manner as 68b from 2-[4-(4-chloro-butoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole (0.458 g, 1.09 mM), diisopropylamine (8.00g, 79 mM), NaI (0.082g, 0.55 mM), and NaHCO₃ (0.275 g, 3.27 mM) in 5 mL DMF. The solution was heated to 95° overnight in a sealed tube. Chromatography gave 0.238 g
5 (45%) of diisopropyl-(4-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-butyl)-amine.

¹H NMR (DMSO-d6) δ7.9 (d, 2H, J=9 Hz), 7.2 (t, 2H, J=8 Hz), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 4H), 4.1 (m, 2H), 3.0 (m, 4H), 2.4 (m, 2H), 1.7 (m, 2H), 1.5 (m, 2H), 0.9 (m, 12H). IR (KBr, cm⁻¹) 1615, 1504, 1255, 1174, 833. MS (ESI) m/e 484.
10 Anal. Calcd for C₂₇H₃₇N₃O₃S₁: C, 67.05; H, 7.71; N, 8.68. Found C, 66.20; H, 7.53; N, 8.57. M.P.=42-44°C. HPLC 100%.

Example 263

Preparation of 2-[4-(3-azetidin-1-yl-propoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole
15



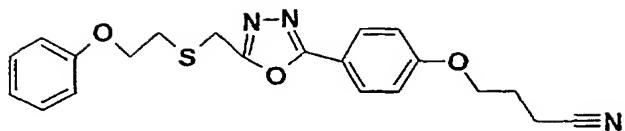
Prepared in a similar manner as 68b from 2-[4-(3-chloro-propoxy)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole (0.348 g, 0.86 mM), azetidine, monohydrochloride, (0.402 g, 4.3 mM), NaI (0.064 g, 0.43 mM), NaHCO₃ (0.433 g, 5.15 mM) in 3 mL DMF. The solution was heated to 95° overnight in a sealed tube.
20 Chromatography and recrystallization from ethyl ether and ethyl acetate gave 30 mg (8%) of the title compound.

¹H NMR (CDCl₃-d6) δ7.9 (d, 2H, J=9 Hz), 7.2 (m, 2H), 7.0 (m, 3), 6.9 (d, 2H, J=8 Hz), 4.2 (t, 2H, J=6 Hz), 4.0 (m, 4H), 3.2 (t, 4H, J=7 Hz), 3.0 (t, 2H, J=6 Hz), 2.6 (t, 2H, J=7 Hz), 2.1 (m, 2H), 1.9 (m, 2H). IR (KBr, cm⁻¹) 2926, 1622, 1603, 1499, 1250, 753.
25 MS (ESI) m/e 426. M.P.=60°C. HPLC 100%.

Example 264

Preparation of 4-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-butyronitrile

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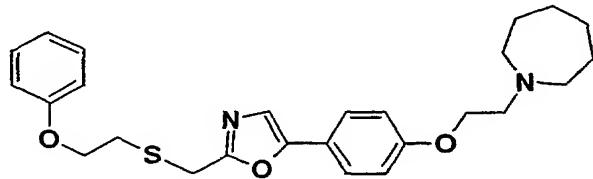
A solution of 4-[5-(2-phenoxyethylsulfanyl methyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.435 g, 1.32 mM), K₂CO₃ (0.492 g, 3.56 mM) and 4-chlorobutyronitrile (0.293 g, 1.98 mM) was heated to 70° in 10 mL DMF for 4 hrs. The resultant mixture was extracted 2 times with ethyl acetate and washed with water, brine, dried over sodium sulfate and concentrated to give 0.452 g crude product. The mixture was purified directly by column chromatography on silica gel (elution with 1/1 ethyl acetate, toluene followed by chloroform/2m ammonia in methanol to give 0.378 g (72%) of the title compound.

¹H NMR (DMSO-d6) δ7.9 (d, 2H, J=9 Hz), 7.2 (t, 2H, J=8 Hz), 7.1 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (m, 6H), 3.0 (t, 2H, J=6 Hz), 2.6 (t, 2H, J=7 Hz), 2.0 (m, 2H). IR (KBr, cm⁻¹) 2930, 1610, 1499, 1464, 1425, 1303, 1253, 1179, 1051, 842, 755. MS (ESI) m/e 396. Anal. Calcd for C₂₁H₂₁N₃O₃S₁: C, 63.78; H, 5.35; N, 10.62. Found C, 60.25; H, 5.13; N, 9.89. M.P.=67-68°C. HPLC 93%.

15

Example 265

Preparation of 1-(2-{4-[2-(2-phenoxyethylsulfanyl methyl)-oxazol-5-yl]-phenoxy}-ethyl)-azepane



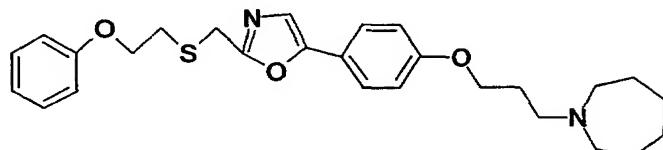
Prepared in a similar manner as 66c from 4-[2-(2-phenoxyethylsulfanyl methyl)-oxazol-5-yl]-phenol (0.461 g, 1.41 mM) and 1-(2-chloro-ethyl)-azepane, monohydrochloride (0.419 g, 2.11 mM) to give 0.196 g (31%) of the title compound.

¹H NMR (DMSO-d6) δ7.6 (d, 2H, J=9 Hz), 7.4 (s, 1H), 7.2 (t, 2H, J=8 Hz), 7.0 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.1 (t, 2H, J=7 Hz), 4.0 (m, 4H), 3.0 (t, 2H, J=6 Hz), 2.8 (m, 2H), 2.7 (m, 4H), 1.5 (m, 8H). IR (KBr, cm⁻¹) 2924, 2822, 1604, 1550, 1502, 1465, 1299, 1251, 1173, 1106, 1029, 818, 750. MS (ESI) m/e 453. Anal. Calcd for C₂₆H₃₂N₂O₃S₁: C, 68.99; H, 7.13; N, 6.19. Found C, 68.84; H, 7.03; N, 6.21. M.P.=35-38°C. HPLC 100%.

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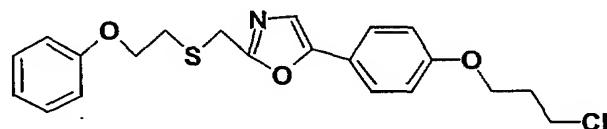
Example 266

Preparation of 1-(3-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenoxy}-propyl)-azepane



5

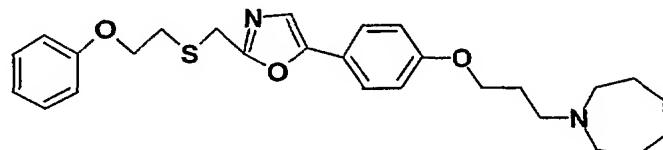
54a) 5-[4-(3-Chloro-propoxy)-phenyl]-2-(2-phenoxy-ethylsulfanylmethyl)-oxazole



Prepared in a similar manner as 68a from 4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenol (1.186 g, 3.62 mM) and 1-bromo-3-chloro-propane (0.855 g, 5.43 mM) to give 0.904 g (62%) of 5-[4-(3-chloro-propoxy)-phenyl]-2-(2-phenoxy-ethylsulfanylmethyl)-oxazole.

¹H NMR (DMSO-d₆) δ7.6 (d, 2H, J=9 Hz), 7.4 (s, 1H), 7.2 (t, 2H, J=8 Hz), 7.0 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.1 (m, 4H), 4.0 (s, 2H), 3.8 (t, 2H, J=6 Hz), 3.0 (t, 2H, J=6 Hz), 2.2 (m, 2H). IR (KBr, cm⁻¹) 2972, 2922, 1603, 1506, 1466, 1295, 1243, 1175, 1105, 1031, 943, 834, 805, 761. MS (ESI) m/e 404. Anal. Calcd for C₂₁H₂₂Cl₁N₁O₃S₁: C, 62.44; H, 5.49; N, 3.47. Found C, 60.66; H, 5.24; N, 3.39. M.P.=71-73°C. HPLC 100%.

54b) 1-(3-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenoxy}-propyl)-azepane



20

Prepared in a similar manner as 68b from 5-[4-(3-chloro-propoxy)-phenyl]-2-(2-phenoxy-ethylsulfanylmethyl)-oxazole (0.400 g, 0.99 mM), azepane (2.45 g, 24.7 mM), NaI (0.074 g, 0.495 mM), and NaHCO₃ (0.22 g, 2.77 mM) in 3 mL DMF. The solution

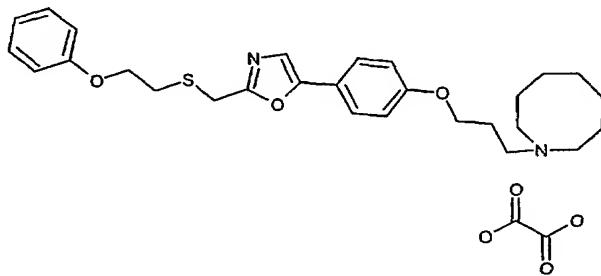
was heated to 90° overnight in a sealed tube. Chromatography and recrystallization from hexane and ethyl ether gave 0.178 g (38%) of the title compound.

¹H NMR (DMSO-d₆) δ7.6 (d, 2H, J=9 Hz), 7.4 (s, 1H), 7.2 (t, 2H, J=8 Hz), 7.0 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.1 (t, 2H, J=7 Hz), 4.0 (m, 4H), 3.0 (t, 2H, J=6 Hz), 2.6 (m, 6H), 1.8 (m, 2H), 1.5 (m, 8H). IR (KBr, cm⁻¹) 2923, 2850, 1602, 1551, 1507, 1465, 1255, 1176, 1110, 1033, 941, 832, 751, 691. MS (ESI) m/e 467. Anal. Calcd for C₂₇H₃₄N₂O₃S₁: C, 69.49; H, 7.34; N, 6.00. Found C, 69.78; H, 7.43; N, 4.09. M.P.=32-35°C. HPLC 100%.

10

Example 267

Preparation of 1-(3-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenoxy}-propyl)-azocane oxalic acid salt

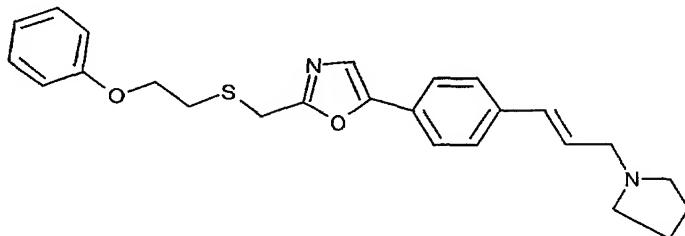


Prepared in a similar manner as 68b from 5-[4-(3-chloro-propoxy)-phenyl]-2-(2-phenoxy-ethylsulfanylmethyl)-oxazole (0.488 g, 1.21 mM), azocane (3.42 g, 30 mM), NaI (0.091 g, 0.495 mM), and NaHCO₃ (0.28 g, 3.39 mM) in 3 mL DMF. The solution was heated to 90° overnight in a sealed tube. Chromatography was followed by formation of the oxalic acid salt. The product mixture was dissolved in acetone (3 mL) and to that was added dropwise a solution of oxalic acid (0.063 g, 0.7 mM) in acetone (2 mL). The mixture was concentrated to low volume and to this was added ethyl ether (5 mL). Upon cooling, a solid precipitated and was collected by filtration and dried under vacuum (40°) to give 0.194 g (28%) of the title compound.

¹H NMR (DMSO-d₆) δ7.6 (d, 2H, J=9 Hz), 7.4 (s, 1H), 7.2 (m, 2H), 7.0 (d, 2H, J=9 Hz), 6.9 (m, 3H), 4.2 (t, 2H, J=7 Hz), 4.1 (t, 2H, J=6 Hz), 4.0 (s, 2H) 3.0 (t, 2H, J=6 Hz), 2.1 (m, 2H), 1.5-1.9 (m, 10H). IR (KBr, cm⁻¹) 2934, 1717, 1601, 1506, 1245, 1203, 1035, 836, 759, 705. MS (ESI) m/e 481. Anal. Calcd for C₃₀H₃₈N₂O₇S₁: C, 63.14; H, 6.71; N, 4.91. Found C, 60.25; H, 6.40; N, 4.64. M.P.=89-94°C. HPLC 80%.

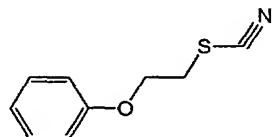
Example 268

Preparation of 2-(2-phenoxy-ethylsulfanylmethyl)-5-[4-(3-pyrrolidin-1-yl-propenyl)-phenyl]-oxazole



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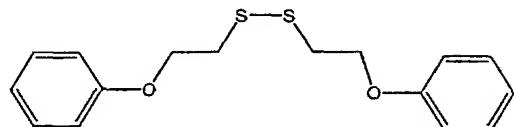
a) (2-Thiocyanato-ethoxy)-benzene



A solution of (2-bromo-ethoxy)-benzene (18.0 g, 89.5 mM) and KSCN (26.1 g, 268 mM) were added together in a nitrogen flushed round bottom flask. The mixture was heated for 3 hours at 100 °C, followed by dilution with H₂O (300 mL), and extraction twice with EtOAc. The combined organic extracts were washed with H₂O (10 X 100 mL), brine (2 X 100 mL), dried over sodium sulfate and concentrated to dryness to give 12.8 g (yellow oil) (80%) of the title compound.

¹H NMR (DMSO-d6) δ7.3 (t, 2H, J=8 Hz), 6.9 (m, 3H), 4.3 (t, 2H, J=5 Hz), 3.5 (t, 2H, J=5 Hz). IR (CHCl₃, cm⁻¹) 3669, 3520, 3016, 2923, 2870, 2158, 1670, 1601, 1497, 1465, 1385, 1303, 1236, 1083, 1038. MS (ESI) m/e 179. Anal calcd. C₉H₉NOS: C, 60.31; H, 5.06; N, 7.81. Found C, 60.11; H, 5.06; N, 7.53. HPLC 100%.

b) Dimer of 2-phenoxy-ethanethiol



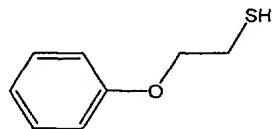
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To a solution of (2-thiocyanato-ethoxy)-benzene (12.8 g, 71.4 mM) in MeOH (200 mL) was added a dropwise solution of NaOMe (70 mL, 321 mM, 25% NaOMe in MeOH) over 25 min. The reaction mixture was stirred for 2.5 hours. The mixture was then

filtered and the collected solid was dried under vacuum overnight to give a white solid, 7.9 g (72%)

¹H NMR (DMSO-d₆) δ 7.3 (t, 2H, J=8 Hz), 6.9 (m, 3H), 4.2 (t, 2H, J=6 Hz), 3.1 (m, 2H). IR (CHCl₃, cm⁻¹) 1600, 1587, 1497, 1243, 1225, 1173, 1032, 1016. MS (ESI) m/e 306. Anal. Calcd for C₁₆H₁₈O₂S₂: C, 62.71; H, 5.92; N, 0.00. Found C, 61.28; H, 5.76; N, 0.72. M.P.=72-75°C. HPLC 100%.

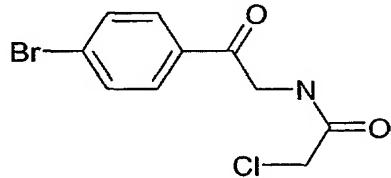
c) 2-Phenoxy-ethanethiol



A solution of the dimer of 2-phenoxy-ethanethiol (6.3 g, 20.4 mM) and Zn dust (12 g, 184 mM) was refluxed in acetic acid (120 mL) for 2 hours. The mixture was diluted with H₂O (300 mL), extracted with dichloromethane, dried over sodium sulfate, filtered and concentrated to dryness to give 5.2 g (83%) of 2-phenoxy-ethanethiol.

¹H NMR (DMSO-d₆) δ 7.3 (t, 2H, J=8 Hz), 6.9 (m, 3H), 4.0 (t, 2H, J=6 Hz), 2.8 (m, 2H).

d) N-[2-(4-Bromo-phenyl)-2-oxo-ethyl]-2-chloro-acetamide



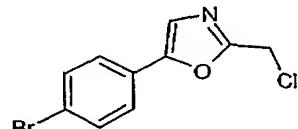
A CH₂Cl₂ suspension (100 mL) of 4-bromophenacylamine hydrochloride (10g, 39.92 mmol, 1 eq.) and chloroacetyl chloride (6.76 g, 59.88 mmol, 1.5 eq.) was treated with 100 mL of triethylamine (12.12 g, 119.76 mmol, 3 eq.) in CH₂Cl₂ dropwise over 1.5 hours. After addition had ceased, the reaction was allowed to stir overnight at room temperature.

The reaction was washed with 0.1 M aqueous HCl and then brine. The organic layer was collected, dried over MgSO₄, filtered, and the solvent removed in vacuo leaving a dark brown oil which was purified via normal phase chromatography using a step

gradient of EtOAc in hexanes as the mobile phase giving 8.38 g (72% yield) of a yellow solid.

¹H NMR (DMSO-d₆) δ 8.56 (t, 1H, J=5 Hz), 7.93 (d, 2H, J=8 Hz), 7.76 (d, 2H, J=8 Hz), 4.66 (m, 2H), 4.20 (s, 2H). IR (CHCl₃, cm⁻¹) 3397, 3009, 1672, 1590, 1526, 5 1074, 987. MS (ES⁺) m/z 290, 292 [M+H]⁺. MS (ES⁻) m/z 288, 290 [M-H]⁻. Anal. Calcd for C₁₀H₉BrClNO₂: C, 41.34; H, 3.12; N, 4.82. Found C, 41.23; H, 2.95; N, 4.75. M.P.=145-146°C.

e) 5-(4-Bromo-phenyl)-2-chloromethyl-oxazole

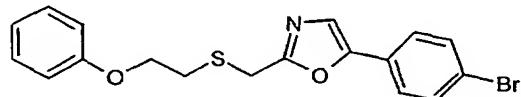


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A POCl₃ suspension (70 mL) of N-[2-(4-bromo-phenyl)-2-oxo-ethyl]-2-chloro-acetamide (7.38 g, 25.4 mmol, 1 eq) was refluxed for 2 hours. The cooled solution was poured into ice and stirred for several hours. The aqueous layer was extracted with EtOAc. The organic layer was collected, dried over MgSO₄, filtered, and the solvent removed in vacuo leaving a dark brown oil which was purified by normal phase chromatography using a gradient of EtOAc in hexanes as the mobile phase leaving 5-(4-bromo-phenyl)-2-chloromethyl-oxazole (5.85 g, 85% yield) as a light brown solid.

¹H (DMSO-d₆) δ 7.8 (s, 1H), 7.7 (m, 4H), 4.9 (s, 2H). IR (CHCl₃, cm⁻¹) 3005, 1481, 1405, 1216, 1119, 1074, 1011, 823. MS (ES⁺) m/z 272, 274 [M+H]⁺. Anal. calcd. for C₁₀H₇BrClNO C, 44.07; H, 2.59; N, 5.14. Found C, 44.06; H, 2.41; N, 5.04.

f) 5-(4-Bromo-phenyl)-2-(2-phenoxy-ethylsulfanylmethyl)-oxazole

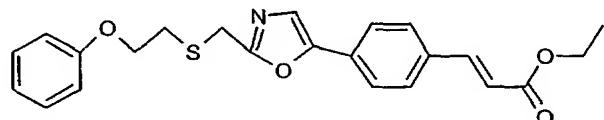


A solution of 2-phenoxy-ethanethiol (3.3 g, 21.39 mmol, 1 eq.) and 5-(4-bromo-phenyl)-2-chloromethyl-oxazole (5.83 g, 21.39 mmol, 1 eq.) in anhydrous DMF was treated with solid potassium carbonate (8.87 g, 64.17 mmol, 3 eq.) and allowed to stir overnight. Diluted the reaction with water and extracted 2x250 mL with EtOAc. The organic layers were combined, washed with 50% brine, collected, dried over MgSO₄,

filtered, and the solvent removed in vacuo leaving a tan solid which was purified by normal phase chromatography using a step gradient of EtOAc in hexanes as the mobile phase leaving 8.16 g (98% yield) of a tan solid.

¹H NMR (DMSO-d6) δ 7.65 (m, 5H), 7.27 (m, 2H), 6.93 (m, 3H), 4.16 (t, 2H, J=7 Hz), 4.06 (s, 2H), 3.00 (t, 2H, J=7 Hz). IR (CHCl₃, cm⁻¹) 3009, 2930, 2871, 1601, 1497, 1481, 1243, 1073, 822. MS (ES⁺) m/z 390, 392 [M+H]⁺. Anal. Calcd. for C₁₈H₁₆BrNO₂S C, 55.39; H, 4.13; N, 3.59. Found C, 55.31; H, 4.03; N, 3.60. M.P.=82-84°C.

10 g) 3-{4-[2-(2-Phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenyl}-acrylic acid ethyl ester

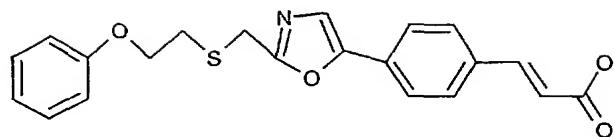


To a closed reaction vessel was added 5-(4-bromo-phenyl)-2-(2-phenoxy-ethylsulfanylmethyl)-oxazole (1.372 g, 3.52 mM), triethylamine (0.427 g, 4.22 mM), Hartwig's ligand¹ (0.126 g, 0.178 mM), bis(dibenzylideneacetone)palladium (0.051 g, 0.088 mM), and ethyl acrylate (0.49 g, 4.93 mM) in DMF (5 mL). The mixture was heated overnight at 80°C, filtered through celite, and concentrated to low volume. The crude reaction mixture was diluted with ethyl acetate and water and separated. The aqueous mixture was extracted with ethyl acetate and the organic extracts combined, which were then washed with water, brine, dried over sodium sulfate, and concentrated to dryness. The residue was purified directly by column chromatography on silica gel (elution with 20% ethyl acetate/hexane followed by 30% ethyl acetate/hexane to give 1.097 g (76%) 55g.

¹H NMR (DMSO-d6) δ 7.8 (d, 2H, J=8 Hz), 7.7-7.6 (m, 4H), 7.3 (t, 2H, J=8 Hz), 6.9 (m, 3H), 6.7 (d, 1H, J=16 Hz), 4.2 (m, 4H), 4.1 (s, 2H), 3.0 (t, 2H, J=7 Hz), 1.3 (t, 3H, J=7 Hz). MS (ESI) m/e 409.8. Anal. Calcd for C₂₃H₂₃N₁O₄S₁: C, 67.46; H, 5.66; N, 3.42. Found C, 66.03; H, 5.54; N, 3.28. M.P.=65-67°C. HPLC 100%.

h) 3-{4-[2-(2-Phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenyl}-acrylic acid

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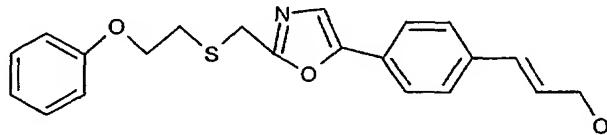


A solution of 3-{4-[2-(2-phenoxyethylsulfanyl)methyl]oxazol-5-yl}-phenyl-acrylic acid ethyl ester (2.323 g (5.67 mM), in 1N NaOH (12 mL, 11.9 mM), EtOH (19 mL), and THF (20 mL) was stirred overnight at room temperature. The reaction mixture
5 was concentrated to low volume and diluted with ethyl acetate/H₂O. The aqueous material was acidified with 1N HCl and extracted with ethyl acetate (4 X 100 mL). The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated to dryness to give 1.082 g (50%) of 3-{4-[2-(2-phenoxyethylsulfanyl)methyl]oxazol-5-yl}-phenyl-acrylic acid

10 ¹H NMR (DMSO-d6) δ7.3 (t, 2H, J=8 Hz), 6.9 (m, 3H), 4.2 (t, 2H, J=6 Hz), 3.1 (m, 2H). IR (KBr, cm⁻¹) 3437, 2928, 1681, 1604, 1499, 1422, 1258, 1220, 1171, 829, 747. MS (ESI) m/e 382. Anal. Calcd for C₂₁H₁₉NO₄S₁: C, 66.12; H, 5.02; N, 3.67. Found C, 65.99; H, 5.21; N, 3.35. M.P.=150-153°C. HPLC 100%.

i)

15 ii) 3-{4-[2-(2-Phenoxyethylsulfanyl)methyl]oxazol-5-yl}-phenyl-prop-2-en-1-ol



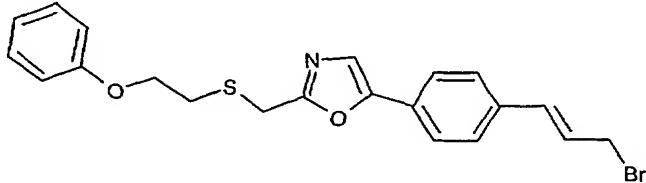
A solution of 3-{4-[2-(2-phenoxyethylsulfanyl)methyl]oxazol-5-yl}-phenyl-acrylic acid (1.9 g, 4.98 mM), diethyl chlorophosphate, (1.031 g, 5.98 mM), and triethylamine (1.0 g, 9.96 mM) was stirred at room temperature in THF (155 mL) for 22 hours. The mixture was filtered, washed with THF, and the filtrate concentrated to dryness. The filtrate was redissolved in 120 mL THF and to this mixture was added dropwise over 3 min. a solution of NaBH₄ (0.378 g, 9.96 mM) dissolved in H₂O (5 mL) and THF (20 mL). After stirring at room temperature for 2.5 hours, 1N HCl (10 mL) was added dropwise and the mixture was stirred overnight at room temperature. The mixture
20 was concentrated to low volume, diluted with ethyl acetate, washed with water, 1N HCl, water, sodium bicarbonate, water, brine, dried over sodium sulfate, and concentrated to dryness. The residue was purified directly by column chromatography (elution with ethyl
25 acetate).

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acetate/toluene followed by 95% chloroform/5% 2M ammonia in methanol) to give 0.331 g (18%) of 3-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenyl}-prop-2-en-1-ol.

¹H NMR (DMSO-d6) δ7.6 (d, 3H, J=8 Hz), 7.5 (d, 2H, J=8 Hz), 7.2 (t, 2H, J=8 Hz), 6.9 (m, 3H), 6.5 (d, 1H, J=16 Hz), 6.4 (tt, 1H, J=5 Hz), 4.2 (m, 4H), 4.0 (s, 2H), 3.0 (t, 2H, J=7 Hz). IR (KBr, cm⁻¹) 3431, 2916, 1653, 1601, 1496, 1247, 968, 750. MS (ESI) m/e 368. Anal. Calcd for C₂₁H₂₁NO₃S₁: C, 68.64; H, 5.76; N, 3.81. Found C, 64.83; H, 5.36; N, 3.57. M.P.=73-74°C.

10 j) 5-[4-(3-Bromo-propenyl)-phenyl]-2-(2-phenoxy-ethylsulfanylmethyl)-oxazole

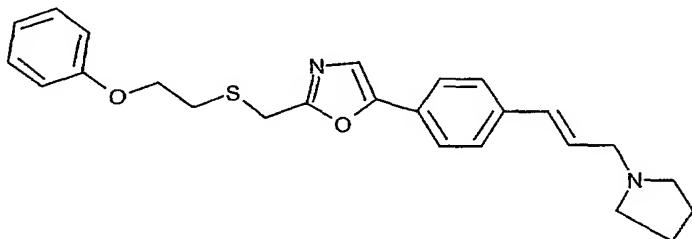


To a solution of triphenylphosphine (0.247 g, 0.943 mM) dissolved in dichloromethane (3 mL) was added bromine (0.151 g, 0.0943 mM) dropwise and the mixture was stirred for 10 min at room temperature. The mixture was cooled to +5°C and 15 a solution of 3-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenyl}-prop-2-en-1-ol (0.333 g, 0.898 mM) and imidazole (0.122 g, 1.8 mM) in dichloromethane (5 mL) was added dropwise. The mixture was stirred at room temperature for 3 hours and washed with water, sodium bicarbonate, water, brine, dried over sodium sulfate and concentrated to dryness. The residue was purified directly by column chromatography on silica gel 20 (elution with 1/3 ethyl acetate/hexane followed by ethyl acetate/toluene to give 0.165 g (43%) of 5-[4-(3-bromo-propenyl)-phenyl]-2-(2-phenoxy-ethylsulfanylmethyl)-oxazole.

¹H NMR (DMSO-d6) δ7.6 (d, 3H, J=7 Hz), 7.5 (d, 2H, J=8 Hz), 7.3 (t, 2H, J=8 Hz), 6.9 (m, 3H), 6.8 (d, 1H, J=16 Hz), 6.6 (m, 1H), 4.4 (d, 2H, J=8 Hz), 4.2 (t, 2H, J=6 Hz), 4.0 (s, 2H), 3.0 (t, 2H, J=7 Hz). IR (KBr, cm⁻¹) 3447, 2923, 2862, 1601, 1546, 1491, 25 1468, 1241, 1204, 1106, 1033, 965, 944, 821, 764, 694, 519. MS (ESI) m/e 432. Anal. Calcd for C₂₁H₂₀BrNO₂S₁: C, 58.61; H, 4.68; N, 3.25. Found C, 59.30; H, 5.03; N, 3.05. M.P.=88-91°C.

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- k) 2-(2-phenoxy-ethylsulfanylmethyl)-5-[4-(3-pyrrolidin-1-yl-propenyl)-phenyl]-oxazole



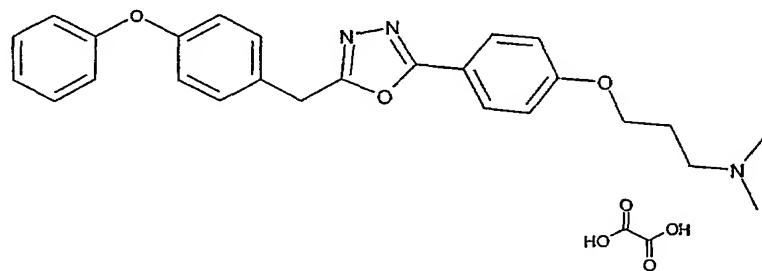
Prepared in a similar manner as 68b from 5-[4-(3-bromo-propenyl)-phenyl]-2-(2-phenoxy-ethylsulfanylmethyl)-oxazole (0.150 g, 0.348 mM), pyrrolidine (1.73 g, 24.4 mM), NaI (0.026 g, 0.174 mM), and NaHCO₃ (0.088 g, 1.04 mM) in 3 mL DMF. Chromatography and recrystallization from ethyl ether and hexane gave 0.044 g (30%) of the title compound.

¹H NMR (DMSO-d6) δ7.6 (d, 3H, J=7 Hz), 7.5 (d, 2H, J=8 Hz), 7.2 (t, 2H, J=8 Hz), 6.9 (m, 3H), 6.6 (d, 1H, J=16 Hz), 6.4 (m, 1H), 4.2 (t, 2H, J=7 Hz), 4.1 (s, 2H), 3.2 (d, 2H, J=7 Hz), 3.0 (t, 2H, J=7 Hz), 1.7 (m, 4H). IR (KBr, cm⁻¹) 2957, 2912, 2778, 1604, 1501, 1463, 1255, 1107, 1056, 973, 944, 822, 754, 693. MS (ESI) m/e 421. Anal. Calcd for C₂₅H₂₈N₂O₂S₁: C, 71.40; H, 6.71; N, 6.66. Found C, 70.88; H, 6.68; N, 6.57. M.P.=73-75°C.

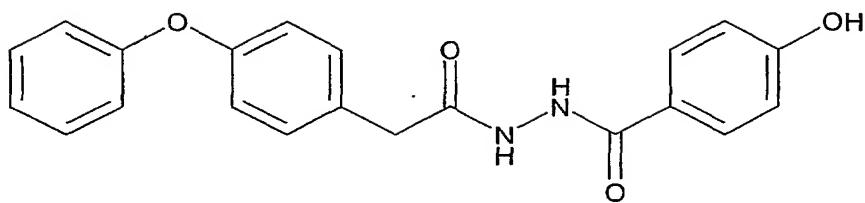
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Example 269

Preparation of Dimethyl-(3-{4-[5-(4-phenoxy-benzyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine, oxalic acid salt



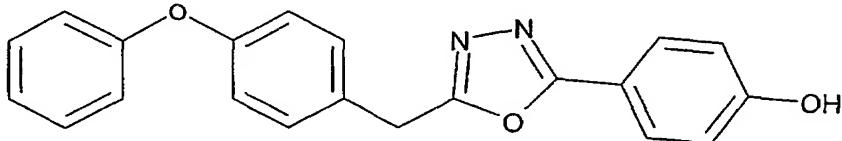
- a) 4-Hydroxy-benzoic acid N'-[2-(4-phenoxy-phenyl)-acetyl]-hydrazide



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 51a, from 4-phenoxyphenylacetic acid (1.16 g, 5.0 mM) to afford 1.59 g (87%) of 4-Hydroxy-benzoic acid N'-(2-(4-phenoxy-phenyl)-acetyl)-hydrazide as a white solid (MP 181-183 °C, MW 362.39).

¹H NMR (DMSO-d₆) δ 10.04 (m, 3H), 7.72 (d, 2H, J=8 Hz), 7.35 (d, 2H, J=8 Hz), 7.33 (d, 2H, J=9 Hz), 7.11 (t, 1H, J=8 Hz), 6.96 (m, 4H), 6.79 (d, 2H, J=9 Hz), and 3.50 (s, 2H). IR (KBr, cm⁻¹) 3292, 1607, 1576, 1510, 1490, 1311, 1279, 1245, 1172, 848, 755, 693, and 507. MS (ESI) m/e 363, 361. Anal. Calcd for C₂₁H₁₈N₂O₄: C, 69.60; H, 5.01; N, 7.73. Found C, 69.08; H, 4.99; N, 7.73.

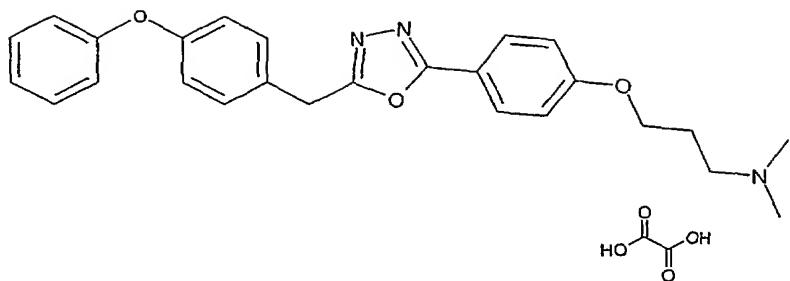
b) 4-[5-(4-phenoxy-benzyl)-[1,3,4]oxadiazol-2-yl]-phenol



The above compound was prepared in a manner similar to that exemplified for the preparation of Example 49e, from 4-Hydroxy-benzoic acid N'-(2-(4-phenoxy-phenyl)-acetyl)-hydrazide (1.53 g, 4.22mM), triphenylphosphine (2.24 g, 8.44 mM), and triethylamine (2.12 mL, 15.19 mM) to afford 0.835 g (57%) of 4-[5-(4-phenoxy-benzyl)-[1,3,4]oxadiazol-2-yl]-phenol as a white solid (MP 202-203 °C, MW 344.37).

¹H NMR (DMSO-d₆) δ 10.24 (s, 1H), 7.77 (d, 2H, J=9 Hz), 7.37 (m, 4H), 7.12 (t, 1H, J=7 Hz), 6.98 (m, 4H), 6.91 (d, 2H, J=9 Hz), and 4.29 (s, 2H). IR (KBr, cm⁻¹) 3124, 2803, 1889, 1610, 1500, 1426, 1366, 1284, 1250, 1172, 1083, 1021, 857, 816, 780, 735, and 691. MS (ESI) m/e 345, 343. Anal. Calcd for C₂₁H₁₆N₂O₃: C, 73.24; H, 4.68; N, 8.13. Found C, 73.08; H, 4.86; N, 8.06.

c) Dimethyl-(3-{4-[5-(4-phenoxy-benzyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine, oxalic acid salt

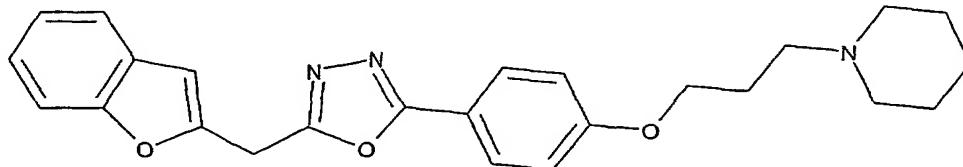


A solution of 4-[5-(4-phenoxy-benzyl)-[1,3,4]oxadiazol-2-yl]-phenol (0.344 g, 1.0 mM), 3-chloro-N,N-dimethylpropylamine hydrochloride (0.174 g, 1.1 mM), and Triton B (40 weight % in CH₃OH, 1.05 mL, 2.3 mM) in 5 mL DMF was stirred at 50-90 °C for 5.5 h. Cesium carbonate (0.066 g, 0.2 mM, 0.4 eq) was then added, and the reaction mixture heated at 90 °C for an additional 4.5 h. The reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate/H₂O. The solvent layers were separated, the aqueous layer back extracted with ethyl acetate, the combined organic extracts washed with water, saturated NaHCO₃ solution, 1N NaOH, and brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford 0.297 g (69%) of a gold gum. Purification by Chromatotron radial chromatography on silica gel (isocratic elution with 95:5 CH₂Cl₂/2.0 M ammonia in methanol) afforded 0.147 g (34%) of Dimethyl-(3-{4-[5-(4-phenoxy-benzyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine as a colorless gum. The gum (0.143 g, 0.33 mM) was dissolved in 2 mL acetone, and oxalic acid (0.033 g, 0.36 mM), dissolved in 1 mL acetone, was added with rapid stirring at room temperature followed by the addition of diethyl ether/hexane (1:2, 3 mL). Filtered the resultant thick precipitate, washed the collected solid with diethyl ether and hexane, and dried in vacuo at 40 °C to afford 0.167 g (97%) of Dimethyl-(3-{4-[5-(4-phenoxy-benzyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine, oxalic acid salt as a white solid (MP 156-158 °C, MW oxalate salt 519.56, MW free amine 429.21).

¹H NMR (DMSO-d₆) δ 7.89 (d, 2H, J=9 Hz), 7.38 (d, 2H, J=8 Hz), 7.36 (d, 2H, J=9 Hz), 7.12 (t, 1H, J=8 Hz), 7.11 (d, 2H, J=9 Hz), 6.99 (d, 2H, J=8 Hz), 6.98 (d, 2H, J=9 Hz), 4.31 (s, 2H), 4.12 (t, 2H, J=6 Hz), 3.15 (t, 2H, J=7 Hz), 2.74 (s, 6H), and 2.09 (m, 2H). IR (KBr, cm⁻¹) 3435, 3034, 2931, 2659, 2562, 1722, 1612, 1589, 1496, 1475, 1428, 1309, 1256, 1169, 1053, 961, 872, 841, 739, 692, and 482. MS (ESI) m/e 430. Anal. Calcd for C₂₆H₂₇N₃O₃·C₂H₂O₄: C, 64.73; H, 5.63; N, 8.09. Found C, 64.11; H, 5.68; N, 7.80. Analytical HPLC: 100% purity.

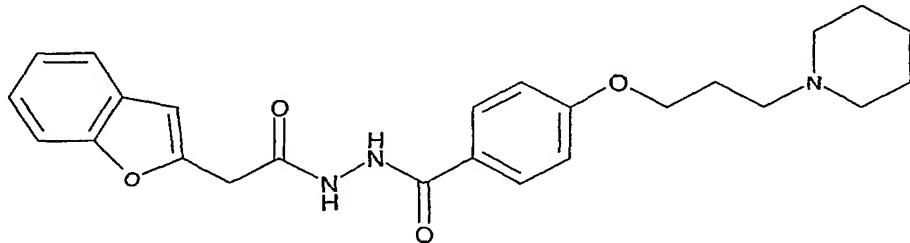
Example 270

Preparation of 1-{3-[4-(5-Benzofuran-2-yl-methyl-[1,3,4]oxadiazol-2-yl)-phenoxy]-propyl}-piperidine



5

a) 4-(3-Piperidin-1-yl-propoxy)-benzoic acid N^t-(2-benzofuran-2-yl-acetyl)-hydrazide



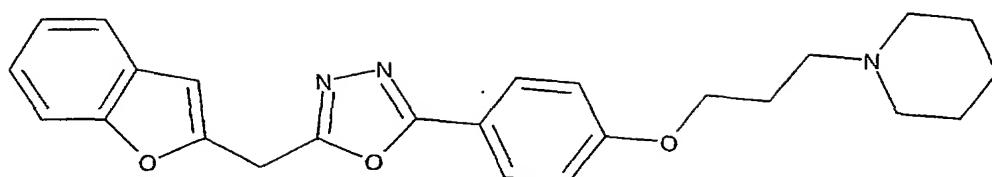
The above compound was prepared in a manner similar to that exemplified for the preparation of Example 51a, from 2-benzofurylacetic acid (0.529 g, 3.0 mM) and 4-(3-piperidin-1-yl-propoxy)-benzoic acid hydrazide (0.749 g, 3.0 mM) followed by purification by column and Chromatotron radial chromatography on silica gel (isocratic elution with 95:5 CH₂Cl₂/2.0 M ammonia in methanol) to afford 0.437 g (33%) of 4-(3-Piperidin-1-yl-propoxy)-benzoic acid N^t-(2-benzofuran-2-yl-acetyl)-hydrazide as an off-white solid (MW 435.53).

15 ¹H NMR (DMSO-d₆) δ 10.28 (s, 1H), 10.21 (s, 1H), 7.83 (d, 2H, J=9 Hz), 7.57 (d, 1H, J=8 Hz), 7.50 (d, 1H, J=8 Hz), 7.22 (m, 2H), 6.99 (d, 2H, J=9 Hz), 6.78 (s, 1H), 4.04 (t, 2H, J=6 Hz), 3.80 (s, 2H), 2.36 (t, 2H, J=7 Hz), 2.31 (m, 4H), 1.86 (m, 2H), 1.47 (m, 4H), and 1.36 (m, 2H). IR (KBr, cm⁻¹) 3234, 2933, 1646, 1606, 1500, 1453, 1304, 1252, 1175, and 750. MS (ESI) m/e 436, 434. Anal. Calcd for C₂₅H₂₉N₃O₄: C, 68.95; H, 6.71; N, 9.65.

20 Found C, 67.82; H, 6.71; N, 9.59.

b) 1-{3-[4-(5-Benzofuran-2-yl-methyl-[1,3,4]oxadiazol-2-yl)-phenoxy]-propyl}-piperidine

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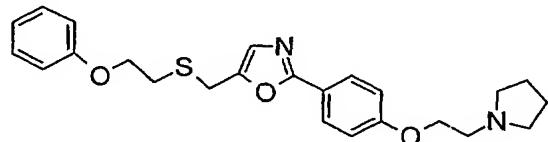


The above compound was prepared in a manner similar to that exemplified for the preparation of Example 49e, from 4-(3-Piperidin-1-yl-propoxy)-benzoic acid N'-(2-benzofuran-2-yl-acetyl)-hydrazide (0.422 g, 0.97 mM), triphenylphosphine (0.514 g, 1.94 mM), and triethylamine (0.487 mL, 3.49 mM) followed by column chromatography purification on silica gel (isocratic elution with ethyl acetate followed by 95:5 CH₂Cl₂/2.0 M ammonia in methanol) to afford 0.129g (31%) of 1-{3-[4-(5-Benzofuran-2-yl-methyl-[1,3,4]oxadiazol-2-yl)-phenoxy]-propyl}-piperidine as a tan solid (MP 76-79 °C, MW 417.51).

¹⁰ ¹H NMR (CDCl₃) δ 7.96 (d, 2H, J=9 Hz), 7.53 (d, 1H, J=8 Hz), 7.45 (d, 1H, J=8 Hz), 7.24 (m, 2H), 6.95 (d, 2H, J=9 Hz), 6.69 (s, 1H), 4.47 (s, 2H), 4.15 (t, 2H, J=6 Hz), 3.09 (m, 2H), 2.47 (m, 2H), and 1.58 (m, 10H). IR (KBr, cm⁻¹) 3439, 2935, 2852, 2806, 2767, 2633, 2545, 1614, 1589, 1500, 1455, 1415, 1305, 1257, 1176, 1123, 1009, 955, 833, 739, 523, and 435. MS (ESI) m/e 418, 416. Anal. Calcd for C₂₅H₂₇N₃O₃: C, 71.92; H, 6.52; N, 10.06. Found C, 67.92; H, 6.28; N, 9.26. Analytical HPLC: 100% purity.

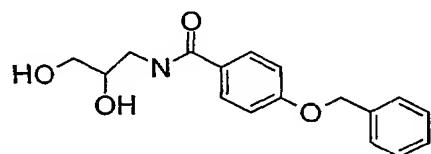
Example 271

Preparation of 5-(2-Phenoxy-ethylsulfanylmethyl)-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-oxazole



²⁰

a) 4-Benzyloxy-N-(2,3-dihydroxy-propyl)-benzamide

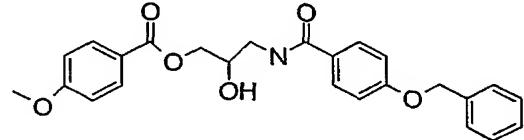


A solution of 4-benzyloxy-benzoic acid (9.08 g, 39.8 mM) and (2,2-dimethyl-[1,3]dioxolan-4-yl)-methylamine (4.97 g, 37.9 mM) in 75 mL methylene chloride was

treated with dicyclohexylcarbodiimide (8.21 g, 39.8 mM) and stirred for 36 h at room temperature. After evaporation of the solvent *in vacuo* the remaining solid was dissolved in 250 mL acidic acid:water (4:1) and warmed to 50 °C for 6 h. The solvents were evaporated and the remaining oil purified by chromatography on silica gel (elution with gradient ethyl acetate/ethanol) to afford a white solid as a mixture of 4-benzyloxy-N-(2,3-dihydroxy-propyl)-benzamide and dicyclohexyl urea. The latter crystallized out of 40 mL ethanol at 5 °C. After evaporation of the solvent 4.0 g (33%) 4-benzyloxy-N-(2,3-dihydroxy-propyl)-benzamide was obtained as an oil.

¹H NMR (DMSO-d₆, 300 MHz) δ 8.23 (t, J=5 Hz, 1H), 7.83 (t, J=8 Hz, 2H), 7.49 – 7.30 (m, 5H), 7.07 (t, J=8 Hz, 2H), 5.18 (s, 2H), 4.80 (br s, 1H), 4.65 (br s, 1H), 3.68 – 3.53 (m, 1H), 3.42 – 3.12 (m, 4H). MS (ESI): m/e = 302 (MH)⁺.

b) 4-Methoxy-benzoic acid 3-(4-benzyloxy-benzoylamino)-2-hydroxy-propyl ester

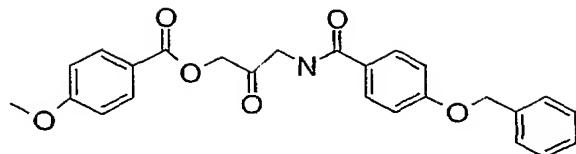


A solution of 4-benzyloxy-N-(2,3-dihydroxy-propyl)-benzamide (4.0 g, 13.27 mM) and triethylamine (4.02 g, 39.82 mM) in 150 mL methylene chloride was cooled to 5 °C and treated with a solution of 4-methoxy-benzoic acid chloride (2.26 g, 13.27 mM) in 50 mL methylene chloride. Within 14 h the reaction mixture was allowed to warm to room temperature and was then quenched with 150 mL water. The organic layer was washed with 10 mL 2M hydrochloric acid, dried over sodium sulfate and evaporated. The remaining oil was purified by chromatography on silica gel (elution with gradient methylene chloride / ethanol) to afford 2.2 g (38%) 4-methoxy-benzoic acid 3-(4-benzyloxy-benzoylamino)-2-hydroxy-propyl ester as a white solid.

¹H NMR (DMSO-d₆, 300 MHz) δ 8.38 (t, J=5 Hz, 1H), 7.96 (t, J=8 Hz, 2H), 7.83 (t, J=8 Hz, 2H), 7.49 – 7.28 (m, 5H), 7.10 – 7.02 (m, 4H), 5.26 (br s, 1H), 5.18 (s, 2H), 4.25 – 3.95 (m, 3H), 3.85 (s, 3H), 3.40 – 3.25 (m, 2H). MS (ESI): m/e = 436 (MH)⁺.

c) 4-Methoxy-benzoic acid 3-(4-benzyloxy-benzoylamino)-2-oxo-propyl ester

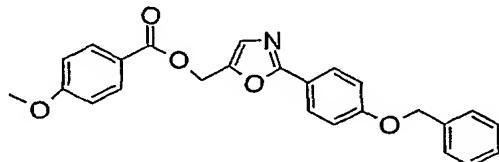
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A solution of 4-methoxy-benzoic acid 3-(4-benzyloxy-benzoylamino)-2-hydroxy-propyl ester (1.2 g, 2.76 mM) in 30 mL methylene chloride was cooled to 5 °C and treated with 7.8 mL of a solution of 1,1-dihydro-1,1,1-triacetoxy-1,2-benziodoxol-3(1H)-one in 5 methylene chloride (Dess-Martin reagent, 15 wt% in methylene chloride, from Acros). After 2 h the reaction mixture was allowed to warm to room temperature and the solvent was removed *in vacuo*. The remains were vigorously stirred with 50 mL of ethyl acetate / *tert*-butylmethyl ether (5 : 1) and filtered. The solution was washed with 20 mL water, dried over sodium sulfate and evaporated to afford 1.0 g (84%) 4-methoxy-benzoic acid 10 3-(4-benzyloxy-benzoylamino)-2-oxo-propyl ester as a white solid.

¹H NMR (CDCl₃, 300 MHz) δ 8.06 (t, J=8 Hz, 2H), 7.82 (t, J=8 Hz, 2H), 7.47 – 7.28 (m, 5H), 7.02 (t, J=8 Hz, 2H), 6.96 (t, J=8 Hz, 2H), 6.82 (br s, 1H), 5.18 (s, 2H), 5.00 (s, 2H), 4.52 (s, 2H), 3.88 (s, 3H). MS (ESI): m/e = 434 (MH)⁺.

15 d) 4-Methoxy-benzoic acid 2-(4-benzyloxy-phenyl)-oxazol-5-ylmethyl ester



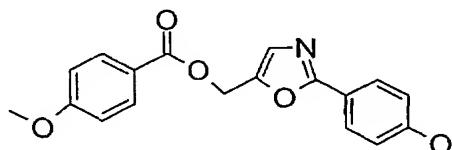
A solution of 4-methoxy-benzoic acid 3-(4-benzyloxy-benzoylamino)-2-oxo-propyl ester (1.0 g, 2.3 mM) in 150 mL anhydrous dioxane in an Argon atmosphere was treated with (methoxycarbonylsulfamoyl)-triethylammonium hydroxide (1.1 g, 4.6 mM) in one portion 20 and heated to 68 °C for 30 minutes. The reaction mixture was poured into 50 mL of water and extracted with 70 mL ethyl acetate.

The organic layer was dried over sodium sulfate and evaporated. The remaining oil was purified by chromatography on silica gel (elution with gradient ethyl acetate/hexane) to afford 320 mg (31%) 4-methoxy-benzoic acid 2-(4-benzyloxy-phenyl)-oxazol-5-ylmethyl ester as a white solid.

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¹H NMR (CDCl₃, 300 MHz) δ 8.01 (t, J=9 Hz, 2H), 7.98 (t, J=9 Hz, 2H), 7.47 – 7.33 (m, 5H), 7.23 (s, 1H), 7.05 (t, J=8 Hz, 2H), 6.92 (t, J=8 Hz, 2H), 5.28 (s, 2H), 5.15 (s, 2H), 3.88 (s, 3H). MS (ESI): m/e = 416 (MH)⁺.

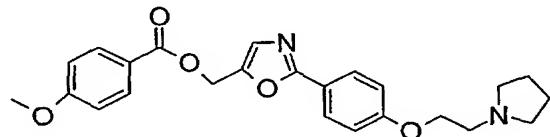
5 e) 4-Methoxy-benzoic acid 2-(4-hydroxy-phenyl)-oxazol-5-ylmethyl ester



A solution of 4-methoxy-benzoic acid 2-(4-benzyloxy-phenyl)-oxazol-5-ylmethyl ester (320 mg, 7.7 mM) in methanol was filled in an autoclave and treated with 10% Palladium on charcoal (32 mg, 3.0 · 10⁻⁵ M). The autoclave was charged with hydrogen (8 bar) and 10 the reaction mixture stirred at 50 °C of 6 h. The pressure was released and the suspension filtered and evaporated to afford 226 mg (90%) of 4-methoxy-benzoic acid 2-(4-hydroxy-phenyl)-oxazol-5-ylmethyl ester as a white solid.

¹H NMR (CDCl₃, 300 MHz) δ 8.02 (t, J=9 Hz, 2H), 7.93 (t, J=9 Hz, 2H), 7.25 (s, 1H), 6.94 – 6.87 (m, 4H), 5.38 (s, 2H), 3.88 (s, 3H). MS (ESI): m/e = 326 (MH)⁺.

15 f) 4-Methoxy-benzoic acid 2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-oxazol-5-ylmethyl ester

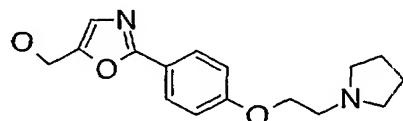


A suspension of 4-methoxy-benzoic acid 2-(4-hydroxy-phenyl)-oxazol-5-ylmethyl ester (220 mg, 0.68 mM), N-(2-chloro-ethyl)-pyrrolidine hydrochloride (115 mg, 0.68 mM), 20 and potassium carbonate (929 mg, 6.72 mM) in 20 mL dimethylformamide was heated at 60°C for 3 h. The solvent was removed *in vacuo* and the remains partitioned between 10 mL water and 30 mL methylene chloride. The organic layer was dried over sodium sulfate and evaporated. The remaining oil was purified by chromatography on silica gel (elution with gradient methylene chloride / ethanol containing 10% ammonia) to afford 100 mg 25 (35 %) of 4-methoxy-benzoic acid 2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-oxazol-5-ylmethyl ester as a white solid.

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¹H NMR (CDCl₃, 300 MHz) δ 7.97 - 7.82 (m, 4H), 7.15 (s, 1H), 6.94 – 6.82 (m, 4H), 5.38 (s, 2H), 4.39 (t, J=6 Hz, 2H), 3.88 (s, 3H), 2.85 (t, J=6 Hz, 2H), 2.63 – 2.52 (m, 4H), 1.80 – 1.70 (m, 4H). MS (ESI): m/e = 423 (MH)⁺.

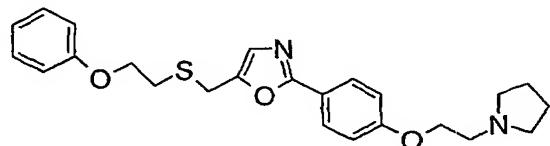
5 g) {2-[4-(2-Pyrrolidin-1-yl-ethoxy)-phenyl]-oxazol-5-yl}-methanol



A solution of 4-methoxy-benzoic acid 2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-oxazol-5-ylmethyl ester (95 mg, 0.23 mM) in anhydrous tetrahydrofuran was treated with lithium aluminium hydride (2 mg, 5.6x10⁻⁵ M) at 5 °C and stirred for 30 minutes. The reaction 10 was quenched with 0.2 mL acetone and evaporated. The remaining oil was dissolved in 75 mL methylene chloride and washed with 50 mL water. The organic layer was dried over sodium sulfate and evaporated and the remaining oil purified by chromatography on silica gel (elution with gradient methylene chloride / ethanol containing 10% ammonia) to afford 15 g (23%) of {2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-oxazol-5-yl}-methanol as a 15 white solid.

¹H NMR (CDCl₃, 300 MHz) δ 7.99 (d, J=9 Hz, 2H), 7.12 (s, 1H), 6.98 (d, J=9 Hz, 2H), 4.75 (s, 2H), 4.45 (t, J=6 Hz, 2H), 4.00 – 3.90 (m, 2H), 3.55 (t, J=6 Hz, 2H), 3.05 – 2.90 (m, 2H), 2.20 – 2.10 (m, 4H). MS (ESI): m/e = 289 (MH)⁺.

20 h) 5-(2-Phenoxy-ethylsulfanylmethyl)-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-oxazole



A solutuion of {2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-oxazol-5-yl}-methanol (6.5 mg, 2.26 x 10⁻⁵ M) and triethylamine (8.2 mg, 8.11 x 10⁻⁵ M) in 2 mL methylene chloride was 25 cooled to 5 °C, treated with methane sulfonyl chloride (2.8 mg, 2.48 x 10⁻⁵ M) in 1 mL methylene chloride and stirred for 30 minutes.

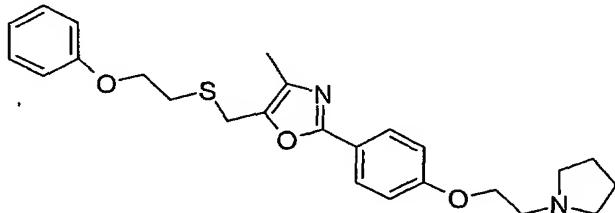
In a separate flask 3 mL ethanol were treated with sodium hydride (8.2 mg, 0.34 mM) at 5 °C, stirred for 10 minutes before 2-phenoxy-ethanethiol (50.2 mg, 0.325 mM) was added. This solution was stirred for further 10 minutes at 5 ° before it was added to the first solution at 5 °C. Stirring of the combined solutions was continued for 72 h. The solvent 5 was evaporated *in vacuo* and the remains were poured into 10 mL water. The aqueous phase was extracted twice with 10 mL methylene chloride. The organic layer was dried over sodium sulfate and evaporated and the remaining oil purified by chromatography on silica gel (elution with gradient methylene chloride / ethanol containing 10% ammonia) to afford 1.5 mg (16%) of 5-(2-phenoxy-ethylsulfanylmethyl)-2-[4-(2-pyrrolidin-1-yl-
10 ethoxy)-phenyl]-oxazole as a white solid.

¹H NMR (CDCl₃, 300 MHz) δ 7.93 (d, J=9 Hz, 2H), 7.30 – 7.27 (m, 2H), 7.01 – 6.88 (m, 6H), 4.25 – 4.14 (m, 4H), 3.95 (s, 2H), 2.98 - 2.89 (m, 4H), 2.72 – 2.60 (m, 4H), 1.88 – 1.78 (m, 4H). MS (ESI): m/e = 425 (MH)⁺.

15

Example 272

Preparation of 4-Methyl-5-(2-phenoxy-ethylsulfanylmethyl)-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-oxazole



a) 2-(4-Methoxy-benzoylamino)-propionic acid methyl ester



20

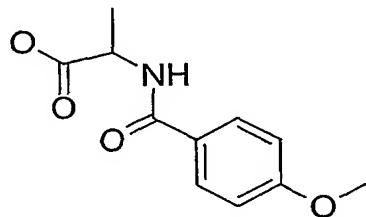
A solution of 4-methoxy-benzoic acid (5.20 g, 34.2 mM) in 35 mL dimethylformamide was cooled to 0 °C and treated with N,N'-carbonyl di-imidazole (5.55 g, 34.2 mM). Stirring was continued for 30 minutes before L-alanine methyl ester hydrochloride (4.68 g, 33.5 mM) was added. The reaction mixture was allowed to warm to room temperature 25 and stirred for 16 h. The solvent was removed *in vacuo* and the remaining oil poured into

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200 mL of 2N HCl and extracted twice with 30 mL methylene chloride. The organic layer was washed twice with 50 mL 5% aqueous Na₂CO₃ solution, dried over sodium sulfate and evaporated to afford 4.28 g (53%) of 2-(4-methoxy-benzoylamino)-propionic acid methyl ester as a white solid.

5 ¹H NMR (CDCl₃, 300 MHz) δ 7.78 (d, J=9 Hz, 2H), 6.94 (d, J=9 Hz, 2H), 6.67 (br s, 1H), 4.80 (q, J=8 Hz, 1H), 3.88 (s, 3H), 3.80 (s, 3H), 1.55 (d, J=8 Hz, 3H). MS (ESI): m/e = 238 (MH)⁺.

b) 2-(4-Methoxy-benzoylamino)-propionic acid



10

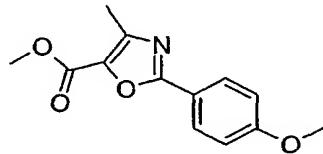
A solution of 2-(4-methoxy-benzoylamino)-propionic acid methyl ester (4.20 g, 17.7 mM) in 20 mL tetrahydrofuran and water (1:1) was treated with lithium hydroxide (0.43 g, 35 mM) and stirred for 20 h at room temperature. The reaction mixture was diluted with 2N HCl until a pH = 1 was reached. The precipitation was filtered and dried to afford 2.5 g (63%) 2-(4-methoxy-benzoylamino)-propionic acid as a white solid.

15

¹H NMR (DMSO-d₆, 300 MHz) δ 12.50 (br s, 1H), 8.48 (d, J=7 Hz, 1H), 7.88 (d, J=9 Hz, 2H), 7.00 (d, J=9 Hz, 2H), 4.42 (q, J=8 Hz, 1H), 3.82 (s, 3H), 1.45 (d, J=8 Hz, 3H). MS (ESI): m/e = 224 (MH)⁺.

20

c) 2-(4-Methoxy-phenyl)-4-methyl-oxazole-5-carboxylic acid methyl ester



A suspension of 2-(4-methoxy-benzoylamino)-propionic acid (1.8 g, 8.0 mM) in 32 mL benzene and 120 mL methylene chloride was treated with oxalyl chloride (10 g, 80 mM) and stirred for 18 h at room temperature. During that time, the suspension turned into a solution. The volatiles were removed *in vacuo*, the remaining oil was cooled to 0 °C and

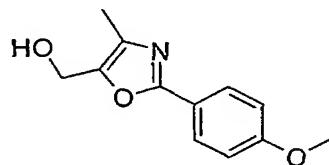
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treated with triethylamine (1.2 g, 12 mM) followed by addition of 60 mL methanol and stirred for 2 h at room temperature. The solvents were removed *in vacuo*. The remains were extracted with *tert*-butyl methyl ether. The ether layer was evaporated and the remaining oil was purified by chromatography on silica gel with methylene chloride to afford 0.82 g (42%) 2-(4-methoxy-phenyl)-4-methyl-oxazole-5-carboxylic acid methyl ester as a white solid.

¹H NMR (CDCl₃, 300 MHz) δ 8.07 (d, J=9 Hz, 2H), 6.98 (d, J=9 Hz, 2H), 3.95 (s, 3H), 3.87 (s, 3H), 2.55 (s, 3H). MS (ESI): m/e = 248 (MH)⁺.

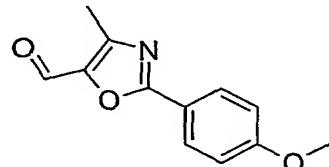
10 d) [2-(4-Methoxy-phenyl)-4-methyl-oxazol-5-yl]-methanol



A solution of 4-(4-methoxy-phenyl)-4-methyl-oxazole-2- carboxylic acid methyl ester (0.79 g, 3.19 mM) in 40 mL toluene was cooled to 0 °C and treated with 7.9 mL di-isobutyl aluminium hydride solution (20% in toluene, 9.58 mM) and stirred for 2 h. The reaction mixture was allowed to warm to room temperature quenched with 5 mL methanol and evaporated. The remaining oil was dissolved in 15 mL methanol and filtered. The methanolic layer was evaporated and the remaining oil purified by chromatography on silica gel (elution with gradient methylene chloride / ethanol) to afford 0.29 g (42%) [2-(4-methoxy-phenyl)-4-methyl-oxazol-5-yl]-methanol as a solid.

20 ¹H NMR (DMSO-d₆, 300 MHz) δ 7.88 (d, J=9 Hz, 2H), 7.06 (d, J=9 Hz, 2H), 5.28 (t, J=7 Hz, 1H), 4.50 (d, J=7 Hz, 2H), 3.95 (s, 3H), 2.25 (s, 3H). MS (ESI): m/e = 220 (MH)⁺.

e) 2-(4-Methoxy-phenyl)-4-methyl-oxazole-5-carbaldehyde

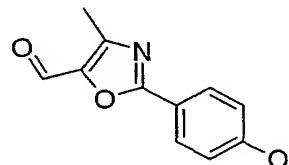


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A solution of [2-(4-methoxy-phenyl)-4-methyl-oxazol-5-yl]-methanol (0.18 g, 0.79 mM) in 3 mL methylene chloride was cooled to 5 °C and treated with 2.5 g of a solution of 1,1-dihydro-1,1,1-triacetoxy-1,2-benziodoxol-3(1H)-one in methylene chloride (Dess-Martin reagent in solution, 15 wt%, from Acros). After 2.5 h the reaction mixture was allowed to 5 warm to room temperature and the solvent was removed *in vacuo*. The remains were vigorously stirred with 50 mL *tert*-butylmethyl ether and filtered. The solution was washed with 10 mL water, dried over sodium sulfate and evaporated to afford 0.16 g (92%) 2-(4-methoxy-phenyl)-4-methyl-oxazole-5-carbaldehyde as an oil.

10 ^1H NMR (CDCl_3 , 300 MHz) δ 9.88 (s, 1H), 8.10 (d, $J=9$ Hz, 2H), 7.00 (d, $J=9$ Hz, 2H), 3.90 (s, 3H), 2.58 (s, 3H). MS (ESI): m/e = 218 (MH^+).

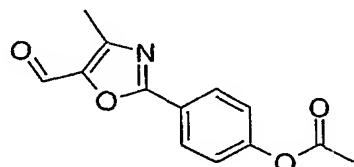
f) 2-(4-Hydroxy-phenyl)-4-methyl-oxazole-5-carbaldehyde



2-(4-Methoxy-phenyl)-4-methyl-oxazole-5-carbaldehyde (0.16 g, 0.73 mM) was dissolved in 4 mL methylene chloride, cooled to -20 °C and treated with 2.58 mL 1M boron tribromide solution in methylene chloride. Within 2 h the reaction mixture was allowed to warm to room temperature and stirred for 28 h. The reaction mixture was quenched with 3 mL water. The organic layer was dried over sodium sulfate and evaporated. The remaining oil was purified by chromatography on silica gel (elution with gradient methylene chloride / ethanol) to afford 63 mg (42%) 2-(4-hydroxy-phenyl)-4-methyl-oxazole-5-carbaldehyde as a white solid.

15 ^1H NMR (CDCl_3 , 300 MHz) δ 9.85 (s, 1H), 8.06 (d, $J=9$ Hz, 2H), 6.95 (d, $J=9$ Hz, 2H), 2.60 (s, 3H). MS (ESI): m/e = 204 (MH^+).

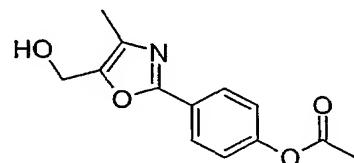
20 25 g) Acetic acid 4-(5-formyl-4-methyl-oxazol-2-yl)-phenyl ester



A solution of 2-(4-hydroxy-phenyl)-4-methyl-oxazole-5-carbaldehyde (63 mg, 0.31 mM) in 1 mL tetrahydrofuran was treated with triethylamine (31.5 mg, 0.31 mM) and acetyl chloride (24.5 mg, 0.31 mM) and stirred at room temperature for 2 h. The solvent was evaporated and the remains dissolved in 4 mL methylene chloride and 4 mL water. The 5 organic layer was dried over sodium sulfate and evaporated to afford 56 mg (74%) acetic acid 4-(5-formyl-4-methyl-oxazol-2-yl)-phenyl ester as a white solid.

¹H NMR (CDCl₃, 300 MHz) δ 9.85 (s, 1H), 8.18 (d, J=9 Hz, 2H), 7.27 (d, J=9 Hz, 2H), 2.58 (s, 3H), 2.35 (s, 3H). MS (ESI): m/e = 246 (MH)⁺.

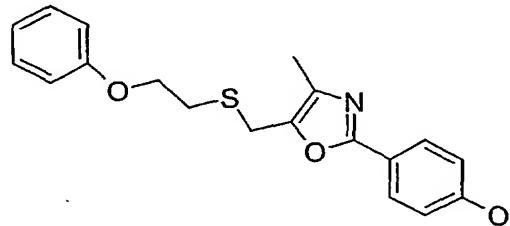
10 h) Acetic acid 4-(5-hydroxymethyl-4-methyl-oxazol-2-yl)-phenyl ester



A solution of acetic acid 4-(5-formyl-4-methyl-oxazol-2-yl)-phenyl ester (56 mg, 0.23 mM) in 5 mL methanol and water (4 : 1) was treated with sodium borohydride (0.33 mg, 8.6x10⁻⁵ M) at 0 °C and stirred for 30 minutes. The reaction was quenched with 0.2 mL 15 acetone and evaporated. The remaining oil was dissolved in 7 mL methylene chloride and washed with 5 mL water. The organic layer was dried over sodium sulfate and evaporated and the remaining oil purified by chromatography on silica gel (elution with gradient methylene chloride / ethanol) to afford 31.5 mg (55%) acetic acid 4-(5-hydroxymethyl-4-methyl-oxazol-2-yl)-phenyl ester as a white solid.

20 ¹H NMR (CDCl₃, 300 MHz) δ 8.05 (d, J=9 Hz, 2H), 7.18 (d, J=9 Hz, 2H), 4.70 (s, 2H), 2.48 (s, 3H), 2.27 (s, 3H). MS (ESI): m/e = 248 (MH)⁺.

i) 4-[4-Methyl-5-(2-phenoxy-ethylsulfanylmethyl)-oxazol-2-yl]-phenol

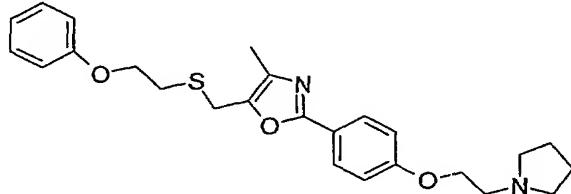


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A solution of acetic acid 4-(5-hydroxymethyl-4-methyl-oxazol-2-yl)-phenyl ester (120 mg, 0.49 mM) and triethylamine (54 mg, 0.53 mM) in 2 mL methylene chloride was cooled to 5 °C, treated with methane sulfonyl chloride (61 mg, 0.53 mM) in 1 mL methylene chloride and stirred for 30 minutes.

- 5 In a separate second flask 8 mL ethanol were treated with sodium hydride (42 mg, 1.75 mM) at 5°C, stirred for 10 minutes before 2-phenoxy-ethanethiol (270 mg, 1.75 mM) was added. This solution was stirred for further 10 minutes at 5 ° before the two separate solutions were combined at that temperature through addition of second solution to the first one. Stirring of the combined solutions was continued for 72 h. The solvent was
10 evaporated *in vacuo* and the remains were poured into 10 mL water. The aqueous phase was extracted with methylene chloride. The organic layer was dried over sodium sulfate and evaporated and the remaining oil purified by chromatography on silica gel (elution with gradient methylene chloride / ethanol) to afford 96 mg (53%) 4-[4-methyl-5-(2-phenoxy-ethylsulfanylmethyl)-oxazol-2-yl]-phenol as a white solid.
15 ^1H NMR (CDCl_3 , 300 MHz) δ 7.83 (d, $J=9$ Hz, 2H), 7.32 – 7.22 (m, 2H), 7.00 – 6.80 (m, 5H), 4.20 (t, $J=7$ Hz, 2H), 3.92 (s, 2H), 2.92 (t, $J=7$ Hz, 2H), 2.27 (s, 3H). MS (ESI): m/e = 342 (MH^+).

- j) 4-Methyl-5-(2-phenoxy-ethylsulfanylmethyl)-2-[4-(2-pyrrolidin-1-yl-ethoxy)-
20 phenyl]-oxazole



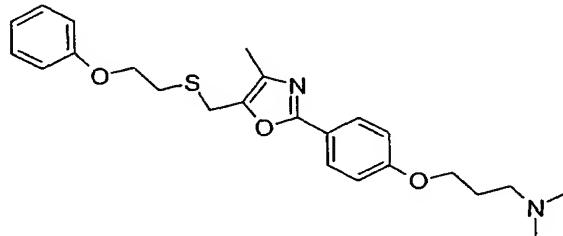
- A suspension of 4-[4-methyl-5-(2-phenoxy-ethylsulfanylmethyl)-oxazol-2-yl]-phenol (57 mg, 0.17 mM), N-(2-chloro-ethyl)-pyrrolidine hydrochloride (31 mg, 0.18 mM), and
25 potassium carbonate (51 mg, 0.37 mM) in 5 mL dimethylformamide was heated at 80°C for 16 h. The solvent was removed *in vacuo* and the remains partitioned between 2 mL water and 5 mL methylene chloride. The organic layer was dried over sodium sulfate and evaporated. The remaining oil was purified by chromatography on silica gel (elution with

gradient methylene chloride / ethanol containing 10% ammonia) to afford 39 mg (53 %) 4-methyl-5-(2-phenoxy-ethylsulfanylmethyl)-2-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-oxazole as a white solid.

¹H NMR (CDCl₃, 300 MHz) δ 7.93 (d, J=9 Hz, 2H), 7.33 – 7.25 (m, 2H), 7.01 – 6.88 (m, 5H), 4.25 – 4.10 (m, 4H), 3.95 (s, 2H), 2.98 – 2.89 (m, 4H), 2.70 – 2.55 (m, 4H), 2.23 (s, 3H), 1.88 – 1.77 (m, 4H). MS (ESI): m/e = 439 (MH)⁺.

Example 273

Preparation of Dimethyl-(3-{4-[4-methyl-5-(2-phenoxy-ethylsulfanylmethyl)-oxazol-2-yl]-phenoxy}-propyl)-amine



A suspension of 4-[4-methyl-5-(2-phenoxy-ethylsulfanylmethyl)-oxazol-2-yl]-phenol (26 mg, 0.08 mM), (3-chloro-propyl)-dimethyl-amine hydrochloride (13.2 mg, 0.08 mM), and potassium carbonate (23 mg, 0.17 mM) in 5 mL dimethylformamide was heated at 80°C for 16 h. The solvent was removed *in vacuo* and the remains partitioned between 2 mL water and 5 mL methylene chloride. The organic layer was dried over sodium sulfate and evaporated. The remaining oil was purified by chromatography on silica gel (elution with gradient methylene chloride / ethanol containing 10% ammonia) to afford 17 mg (52 %) dimethyl-(3-{4-[4-methyl-5-(2-phenoxy-ethylsulfanylmethyl)-oxazol-2-yl]-phenoxy}-propyl)-amine as a white solid.

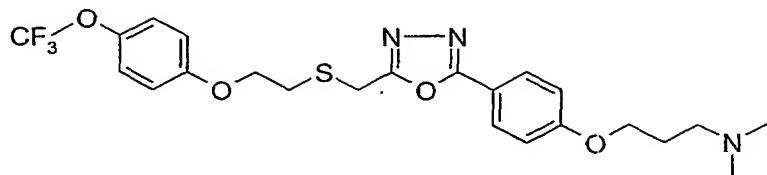
¹H NMR (CDCl₃, 300 MHz) δ 7.91 (d, J=9 Hz, 2H), 7.33 – 7.24 (m, 2H), 7.00 – 6.87 (m, 5H), 4.20 (t, J=7 Hz, 2H), 4.08 (t, J=7 Hz, 2H), 3.92 (s, 2H), 2.95 (t, J=7 Hz, 2H), 2.48 (t, J=7 Hz, 2H), 2.28 (s, 6H), 2.22 (s, 3H), 2.02 – 1.92 (m, 2H). MS (ESI): m/e = 428 (MH)⁺.

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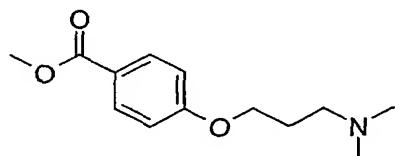
Example 274

Preparation of [3-(4-{5-[2-(4-trifluoromethoxy-phenoxy)-ethylsulfanylmethyl]-[1,3,4]oxadiazol-2-yl}-phenoxy)-propyl]-dimethyl-amine

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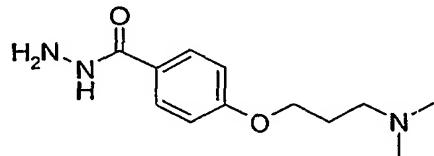
a) Methyl 4-(3-dimethylamino-propoxy)-benzoate



To a cold mixture (0 °C) of methyl 4-hydroxybenzoate (33.93 g, 223 mmol), 5 triphenylphosphine (53.29 g, 203 mmol), and 3-dimethylaminopropanol-1 (20.88 g, 202 mmol) in anhydrous THF (180 mL) was added diisopropylazodicarboxylate (44 mL, 223 mmol) over 5 minutes with stirring. The stirring continued at 0 °C for 30 minutes and then 23 °C overnight. After removal of solvent, the residue was submitted to a flash filtration chromatography on silica gel (elution with ethyl acetate, then 20% 2M NH₃-10 MeOH in CH₂Cl₂). A yellowish oil was obtained (44.83 g, 94%).

¹H NMR (CDCl₃) δ 7.95 (d, 2H, J=8.85 Hz), 6.88 (d, 2H, J=8.85 Hz), 4.04 (t, 2H, J=6.55 Hz), 3.85 (s, 3H), 2.42 (t, 2H, J=7.26 Hz), 2.22(s, 6H), 1.94 (m, 2H, J=6.55, 7.26 Hz). MS (ES⁺) m/e 238.

15 b) 4-(3-Dimethylamino-propoxy)-benzoic hydrazide

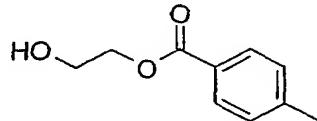


A mixture of methyl 4-(3-dimethylamino-propoxy)-benzoate (44.83 g, 189 mmol) and hydrazine monohydrate (100 g, 2000 mmol) was stirred at 80 °C overnight; then it was allowed to cool to 23 °C. A white solid formed. The solid was collected by 20 filtration, washed with hexanes (3 × 50 mL), and dried in vacuum to afford a white powder (32.01 g, 71%).

¹H NMR (CDCl₃) δ 7.67 (d, 2H, J=8.85 Hz), 6.90 (d, 2H, J=8.85 Hz), 7.36 (s, b, 1H), 4.02 (t, 2H, J=6.37 Hz), 4.00 (s, b, 2H), 2.42 (t, 2H, J=7.26 Hz), 2.22(s, 6H), 1.93 (m, 2H,

J=6.37, 7.26 Hz). MS (ES⁺) m/e 238. mp 79.5-81.0 °C. Anal. Calcd for C₁₂H₁₉N₃O₂: C, 60.74; H, 8.07; N, 17.71. Found C, 60.39; H, 7.97; N, 17.63.

c) Ethylene glycol mono-*p*-toluate

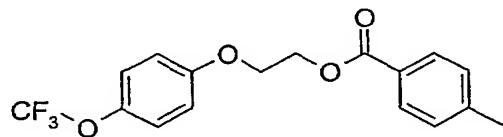


5

To a cold solution (0 °C) of triethylamine (40 mL, 287 mmol) and ethylene glycol (60 mL, 1080 mmol) in dichloromethane (300 mL) was added *p*-toluoyl chloride (27 mL, 200 mmol) with stirring. After 30 minutes, cooling bath was removed and stirring continued overnight at 23 °C. The reaction mixture was distributed between diethyl ether (300 mL) and water (300 mL). The organic phase was isolated and washed subsequently with 0.3 N HCl (aq, 200 mL), sat. NaHCO₃ (aq, 200 mL), and sat. NaCl (aq, 200 mL). After removal of solvent, the residue was purified on a silica gel column with hexanes-ethyl acetate (3:1) to give a white solid (29.34 g, 81.4%).

10 ¹H NMR (CDCl₃) δ 7.92 (d, 2H, J=8.49 Hz), 7.22 (d, 2H, J=7.78 Hz), 4.41-4.45
15 (m, 2H), 3.94 (q, 2H, J=5.83, 9.37 Hz), 2.39 (s, 3H), 2.03 (t, 2H, J=5.83 Hz). MS (ES⁺)
m/e 181. mp 44.5-45.0 °C.

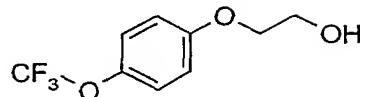
d) 2-(4-Trifluoromethoxy-phenoxy)-ethyl *p*-toluate



20 To a cold mixture (0 °C) of ethylene glycol mono-*p*-toluate (1.80g, 10 mmol), triphenylphosphine (2.88 g, 11 mmol), and 4-trifluoromethoxyphenol (1.87g, 10.5 mmol) in anhydrous THF (10 mL) was added diisopropylazodicarboxylate (2.2 mL, 10.5 mmol) with stirring. The reaction mixture was stirred at 0 °C for 30 minutes and then 23 °C overnight. After removal of solvent, the residue was purified by chromatography on silica gel (elution with 5% ethyl acetate in hexanes) to provide a white solid (3.06 g, 90%).

25 ¹H NMR (CDCl₃) δ 7.91 (d, 2H, J=8.14 Hz), 7.21 (d, 2H, J=8.14 Hz), 7.13 (d, 2H, J=8.85 Hz), 6.91 (d, 2H, J=8.85 Hz), 4.63 (t, 2H, J=4.77 Hz), 4.27 (t, 2H, J=4.77 Hz), 2.38 (s, 3H). MS (ES⁺) m/e 341. mp 76.0-77.5 °C.

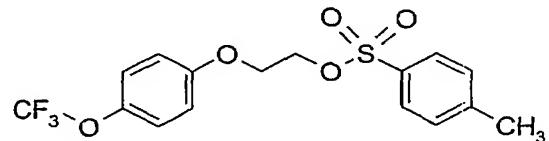
e) 2-(4-Trifluoromethoxy-phenoxy)-ethanol-1



A solution of 2-(4-trifluoromethoxy-phenoxy)-ethyl *p*-toluate (3.06 g, 9 mmol) in 5 2 N LiOH (20 mL, 40 mmol), THF (15 mL), and MeOH (15 mL) was stirred at 23 °C overnight. After neutralized with sat. NaHCO₃ (aq, 100 mL), the reaction mixture was extracted with diethyl ether (3 × 100 mL). The combined organic phases were dried over anhydrous sodium sulfate. After removal of solvent, a colorless oil was obtained (2.00 g, 100%)

10 ¹H NMR (CDCl₃) δ 7.13 (d, 2H, J=9.20 Hz), 6.89 (d, 2H, J=9.20 Hz), 4.05 (t, 2H, J=4.42 Hz), 3.95 (m, b, 2H), 1.96 (t, b, 1H). MS (ES⁺) m/e 223.

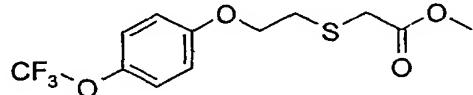
f) 2-(4-Trifluoromethoxy-phenoxy)-ethyl tosylate



15 A cold solution of 2-(4-trifluoromethoxy)-ethanol-1 (667 mg, 3 mmol), pyridine (0.5 mL, 6 mmol), and *p*-toluenesulfonyl chloride (860 mg, 4.5 mmol) in chloroform (5 mL) was stirred at 0 °C. After 6 hours, solvent was removed and the residue was submitted to a silica gel chromatography (elution with 20% ethyl acetate in hexanes) to afford a white solid (858 mg, 76%).

20 ¹H NMR (CDCl₃) δ 7.79 (d, 2H, J=8.14 Hz), 7.31 (d, 2H, J=8.14 Hz), 7.08 (d, 2H, J=9.20 Hz), 6.75 (d, 2H, J=9.20 Hz), 4.34–4.38 (m, 2H), 4.10–4.14 (m, 2H), 2.42 (s, 3H). MS (ES⁺) m/e 377. mp 35.0–36.0 °C.

g) Methyl 2-(4-trifluoromethoxy-phenoxy)-ethylsulfanyl-acetate



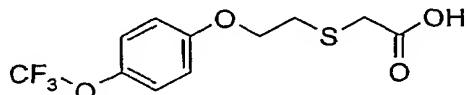
25 A mixture of 2-(4-trifluoromethoxy-phenoxy)-ethyl tosylate (753 mg, 2 mmol), methyl thioglycolate (0.4 mL, 7 mmol), and potassium carbonate (875 mg, 6 mmol) in

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THF (5 mL) was stirred at 65 °C overnight. The reaction mixture was filtered and washed with diethyl ether (3 × 6 mL) and dichloromethane (2 × 6 mL). After evaporation of solvent, the residue was purified by chromatography on silica gel (elution with 20% ethyl acetate in hexanes) to deliver a colorless oil (619 mg, 100%).

5 ¹H NMR (CDCl₃) δ 7.12 (d, 2H, J=9.20 Hz), 6.86 (d, 2H, J=9.20 Hz), 4.15 (t, 2H, J=6.37 Hz), 3.71 (s, 3H), 3.33 (s, 2H), 3.01 (t, 2H, J=6.37 Hz). MS (ES⁺) m/e 311.

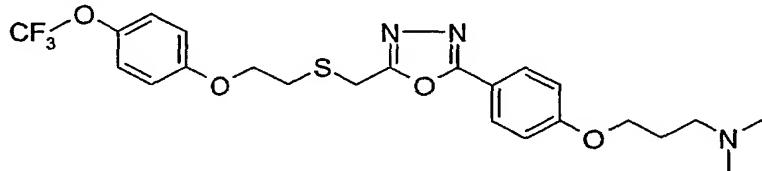
h) 2-(4-Trifluoromethoxy-phenoxy)-ethylsulfanyl acetic acid



10 A solution of methyl 2-(4-trifluoromethoxy-phenoxy)-ethylsulfanyl-acetate (619 mg, 2.0 mmol) in 2 N LiOH (aq, 3 mL), MeOH (3 mL), and THF (3 mL) was stirred at 23 °C. After one hour, the reaction mixture was acidified with 3 N HCl (aq, 4 mL). The aqueous layer was isolated and extracted twice with dichloromethane (25 mL each). The combined organic phases were dried with anhydrous magnesium sulfate. After removal 15 of solvent, a colorless oil was obtained (580 mg, 98%).

1 ¹H NMR (CDCl₃) δ 7.12 (d, 2H, J=9.20 Hz), 6.86 (d, 2H, J=9.20 Hz), 4.17 (t, 2H, J=6.01 Hz), 3.37 (s, 2H), 3.03 (t, 2H, J=6.01 Hz). MS (ES⁻) m/e 295.

i) [3-(4-{5-[2-(4-Trifluoromethoxy-phenoxy)-ethylsulfanylmethyl]-[1,3,4]oxadiazol-2-yl}-phenoxy)-propyl]-dimethyl-amine



To a cold solution (0 °C) of 2-(4-trifluoromethoxy-phenoxy)-ethylsulfanyl acetic acid (296 mg, 1 mmol), 4-(3-dimethylamino-propoxy)-benzoic hydrazide (237 mg, 1 mmol), and triphenylphosphine (1.31 g, 5 mmol) in anhydrous acetonitrile (10 mL) was 25 added a mixture of carbon tetrachloride (0.58 mL, 6 mmol) and triethylamine (0.97 mL, 7 mmol) with stirring. The stirring continued at 0 °C for 30 minutes and then 23 °C overnight. After evaporation of solvent, the residue was distributed between 1N NaOH

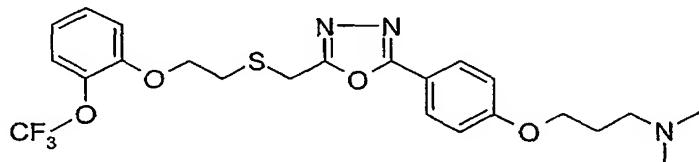
-490-

(30 mL) and dichloromethane (25 mL). The aqueous layer was isolated and extracted twice with dichloromethane (25 mL each). The combined organic phases were dried with anhydrous sodium sulfate. After removal of solvent, the residue was submitted for purification on silica gel (elution with ethyl acetate, then 4% 2 M NH₃-MeOH in dichloromethane) to yield a white solid (267 mg, 54%).

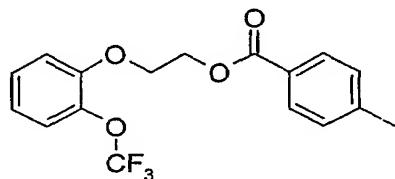
¹H NMR (CDCl₃) δ 7.92 (d, 2H, J=8.85 Hz), 7.09 (d, 2H, J=8.86 Hz), 6.97 (d, 2H, J=8.85 Hz), 6.85 (d, 2H, J=8.86 Hz), 4.15 (t, 2H, J=6.19 Hz), 4.07 (t, 2H, J=6.37 Hz), 4.00 (s, 2H), 3.02 (t, 2H, J=6.19 Hz), 2.45 (t, 2H, J=7.08 Hz), 2.24 (s, 6H), 1.97 (m, 2H, J=6.37, 7.08 Hz). MS (ES⁺) m/e 498. mp 92.5-93.5 °C. Anal. Calcd for C₂₃H₂₆F₃N₃O₄S: C, 55.52; H, 5.27; N, 8.45; S, 6.44; F, 11.46. Found C, 55.29; H, 5.14; N, 8.38; S, 6.28; F, 11.38.

Example 275

Preparation of [3-(4-{5-[2-(2-trifluoromethoxy-phenoxy)-ethylsulfanyl methyl]-[1,3,4]oxadiazol-2-yl}-phenoxy)-propyl]-dimethyl-amine



a) 2-(2-Trifluoromethoxy-phenoxy)-ethyl p-toluate



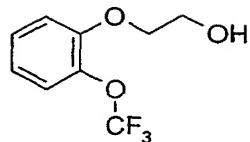
In a similar manner as exemplified in Example 274 part d), 2-trifluoromethoxyphenol (1.87 g, 10.5 mmol) was converted into 2-(2-trifluoromethoxy-phenoxy)-ethyl p-toluate (3.10 g, 87%) as a colorless oil.

¹H NMR (CDCl₃) δ 7.91 (d, 2H, J=8.14 Hz), 7.17-7.26 (m, 4H), 7.02 (dd, 1H, J=1.42, 8.85 Hz), 6.95 (td, 1H, J=1.42, 7.78 Hz), 4.65 (t, 2H, J=4.78 Hz), 4.34 (t, 2H, J=4.78 Hz), 2.38 (s, 3H). MS (ES⁺) m/e 341.

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b) 2-(2-Trifluoromethoxy-phenoxy)-ethanol-1

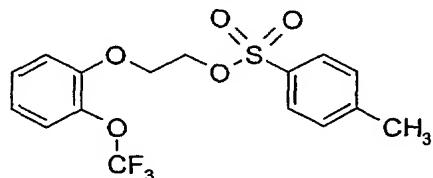
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In a similar manner as exemplified in Example 274 part e), 2-(2-trifluoromethoxy-phenoxy)-ethyl *p*-toluate (2.72 g, 8 mmol) was converted into 2-(2-trifluoromethoxy-phenoxy)-ethanol-1 (1.74 g, 98%) as a colorless oil.

5 ¹H NMR (CDCl₃) δ 7.20-7.27 (m, 2H), 7.69-7.02 (m, 2H), 4.12 (t, 2H, J=4.42 Hz), 3.96 (q, 2H, J=4.95, 9.20), 2.06 (m, b, 1H). MS (ES⁺) m/e 223.

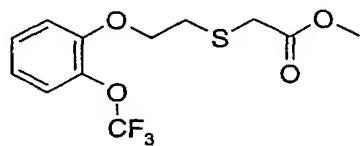
c) 2-(2-Trifluoromethoxy-phenoxy)-ethyl tosylate



10 In a similar manner as exemplified in Example 274 part f), 2-(2-trifluoromethoxy-phenoxy)-ethanol-1 (666 mg, 2 mmol) was converted into 2-(2-trifluoromethoxy-phenoxy)-ethyl tosylate (926 mg, 82%) as a colorless oil.

15 ¹H NMR (CDCl₃) δ 7.79 (d, 2H, J=8.14 Hz), 7.31 (d, 2H, J=8.14 Hz), 7.16-7.22 (m, 2H), 6.95 (t, 1H, J=7.78 Hz), 6.90 (d, 1H, J=7.78 Hz), 4.32-4.36 (m, 2H), 4.18-4.23 (m, 2H), 2.42 (s, 3H). MS (ES⁺) m/e 377.

d) Methyl 2-(2-trifluoromethoxy-phenoxy)-ethylsulfanyl-acetate

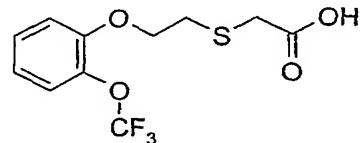


20 In a similar manner as exemplified in Example 274 part g), 2-(2-trifluoromethoxy-phenoxy)-ethyl tosylate (753 mg, 2 mmol) was converted into methyl 2-(2-trifluoromethoxy-phenoxy)-ethylsulfanyl-acetate (620 mg, 100%) as a colorless oil.

1 ¹H NMR (CDCl₃) δ 7.18-7.25 (m, 2H), 6.89-7.00 (m, 2H), 4.22 (t, 2H, J=6.37 Hz), 3.71 (s, 3H), 3.39 (s, 2H), 3.04 (t, 2H, J=6.37 Hz). MS (ES⁺) m/e 311.

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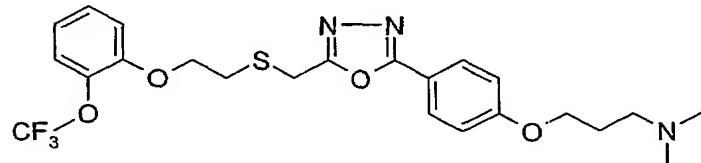
e) 2-(2-Trifluoromethoxy-phenoxy)-ethylsulfanyl acetic acid



In a similar manner as exemplified in Example 274 part h), methyl 2-(2-trifluoromethoxy-phenoxy)-ethylsulfanyl-acetate (620 mg, 2 mmol) was converted into 2-(2-trifluoromethoxy-phenoxy)-ethylsulfanyl acetic acid (592 mg, 100%) as a white solid.

¹H NMR (CDCl₃) δ 7.18-7.26 (m, 2H), 6.92-6.99 (m, 2H), 4.24 (t, 2H, J=6.01 Hz), 3.44 (s, 2H), 3.07 (t, 2H, J=6.01 Hz). MS (ES⁻) m/e 295. mp 41.5-42.5 °C.

f) [3-(4-{5-[2-(2-Trifluoromethoxy-phenoxy)-ethylsulfanylmethyl]-[1,3,4]oxadiazol-2-yl}-phenoxy)-propyl]-dimethyl-amine



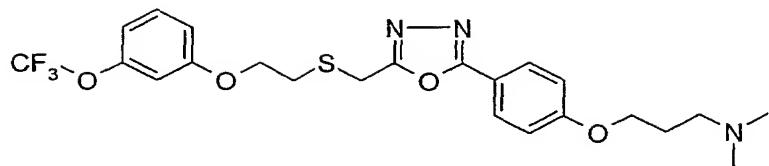
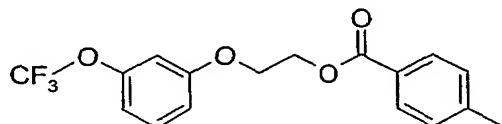
In a similar manner as exemplified in Example 274 part i), 2-(2-trifluoromethoxy-phenoxy)-ethylsulfanyl acetic acid (296 mg, 1 mmol) was converted into [3-(4-{5-[2-(2-trifluoromethoxy-phenoxy)-ethylsulfanylmethyl]-[1,3,4]oxadiazol-2-yl}-phenoxy)-propyl]-dimethyl-amine (320 mg, 64%) as a white solid.

¹H NMR (CDCl₃) δ 7.93 (d, 2H, J=9.20 Hz), 7.18-7.25 (m, 2H), 6.97 (d, 2H, J=9.20 Hz), 6.91-6.96 (m, 2H), 4.24 (t, 2H, J=6.19 Hz), 4.07 (t, 2H, J=6.55 Hz), 4.05 (s, 2H), 3.07 (t, 2H, J=6.19 Hz), 2.45 (t, 2H, J=7.08 Hz), 2.25 (s, 6H), 1.97 (m, 2H, J=6.55, 7.08 Hz). MS (ES⁺) m/e 498. mp 55.0-55.5 °C. Anal. Calcd for C₂₃H₂₆F₃N₃O₄S: C, 55.52; H, 5.27; N, 8.45; S, 6.44; F, 11.46. Found C, 55.28; H, 5.32; N, 8.26; S, 6.48; F, 11.76.

Example 276

Preparation of [3-(4-{5-[2-(3-trifluoromethoxy-phenoxy)-ethylsulfanylmethyl]-[1,3,4]oxadiazol-2-yl}-phenoxy)-propyl]-dimethyl-amine

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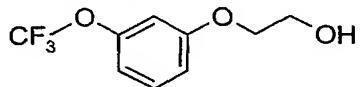
a) 2-(3-Trifluoromethoxy-phenoxy)-ethyl *p*-toluate

In a similar manner as exemplified in Example 274 part d), 3-trifluoromethoxyphenol (1.87 g, 10.5 mmol) was converted into 2-(3-trifluoromethoxy-phenoxy)-ethyl *p*-toluate (3.31 g, 93%) as a white solid.

¹H NMR (CDCl₃) δ 7.92 (d, 2H, J=8.14 Hz), 7.27 (t, 1H, J=8.32 Hz), 7.22 (d, 2H, J=8.14 Hz), 6.77-6.87 (m, 3H), 4.63 (t, 2H, J=4.77 Hz), 4.28 (t, 2H, J=4.77 Hz), 2.39 (s, 3H). MS (ES⁺) m/e 341. mp 63.0-64.0 °C.

10

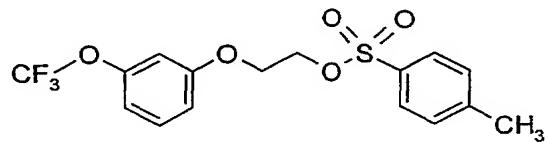
b) 2-(3-Trifluoromethoxy-phenoxy)-ethanol-1



In a similar manner as exemplified in Example 274 part e), 2-(3-trifluoromethoxy-phenoxy)-ethyl *p*-toluate (2.72 g, 8 mmol) was converted into 2-(3-trifluoromethoxy-phenoxy)-ethanol-1 (1.78 g, 100%) as a colorless oil.

¹H NMR (CDCl₃) δ 7.13 (d, 2H, J=8.85 Hz), 6.85-6.94 (m, 2H), 4.05 (t, 2H, J=4.42 Hz), 3.95 (s, b, 2H), 1.96 (s, b, 1H). MS (ES⁺) m/e 223.

c) 2-(3-Trifluoromethoxy-phenoxy)-ethyl tosylate



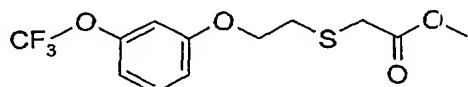
20

In a similar manner as exemplified in Example 274 part f), 2-(3-trifluoromethoxy-phenoxy)-ethanol-1 (666 mg, 2 mmol) was converted into 2-(3-trifluoromethoxy-phenoxy)-ethyl tosylate (1.00 g, 89%) as a white solid.

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¹H NMR (CDCl₃) δ 7.79 (d, 2H, J=8.49 Hz), 7.82 (d, 2H, J=8.49 Hz), 7.23 (t, 1H, J=8.49 Hz), 6.80 (d, 1H, J=8.49 Hz), 6.70 (d, 1H, J=8.49 Hz), 6.58 (s, 1H), 4.34-4.38 (m, 2H), 4.10-4.14 (m, 2H), 2.42 (s, 3H). MS (ES⁺) m/e 377. mp 58.5-59.5 °C.

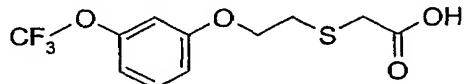
5 d) Methyl 2-(3-trifluoromethoxy-phenoxy)-ethylsulfanyl-acetate



In a similar manner as exemplified in Example 274 part g), 2-(3-trifluoromethoxy-phenoxy)-ethyl tosylate (753 mg, 2 mmol) was converted into methyl 2-(3-trifluoromethoxy-phenoxy)-ethylsulfanyl-acetate (625 mg, 100%) as a colorless oil.

10 ¹H NMR (CDCl₃) δ 7.26 (t, 1H, J=8.49 Hz), 6.80 (d, 2H, J=8.49 Hz), 6.73 (s, 1H), 4.16 (t, 2H, J=6.37 Hz), 3.71 (s, 3H), 3.34 (s, 2H), 3.01 (t, 2H, J=6.37 Hz). MS (ES⁺) m/e 311.

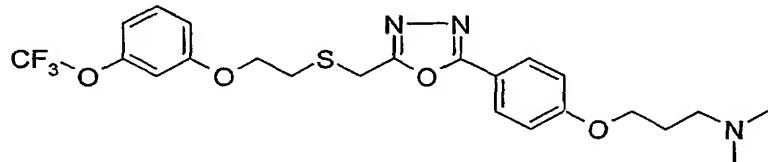
15 e) 2-(3-Trifluoromethoxy-phenoxy)-ethylsulfanyl acetic acid



In a similar manner as exemplified in Example 274 part h), methyl 2-(3-trifluoromethoxy-phenoxy)-ethylsulfanyl-acetate (620 mg, 2 mmol) was converted into 2-(3-trifluoromethoxy-phenoxy)-ethylsulfanyl acetic acid (513 mg, 87%) as a colorless oil.

10 ¹H NMR (CDCl₃) δ 7.26 (t, 1H, J=8.14 Hz), 6.81 (d, 2H, J=8.14 Hz), 6.73 (s, 1H), 4.18 (t, 2H, J=6.01 Hz), 3.38 (s, 2H), 3.04 (t, 2H, J=6.01 Hz). MS (ES⁻) m/e 295.

f) [3-(4-{5-[2-(3-Trifluoromethoxy-phenoxy)-ethylsulfanylmethyl]-[1,3,4]oxadiazol-2-yl}-phenoxy)-propyl]-dimethyl-amine



25 In a similar manner as exemplified in Example 274 part i), 2-(3-trifluoromethoxy-phenoxy)-ethylsulfanyl acetic acid (296 mg, 1 mmol) was converted into [3-(4-{5-[2-(3-

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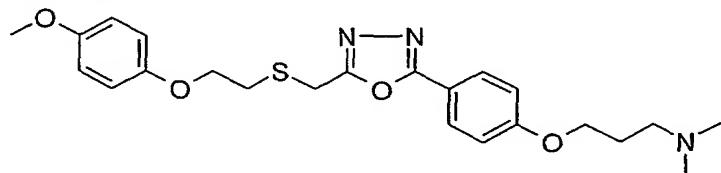
trifluoromethoxy-phenoxy)-ethylsulfanyl methyl]-[1,3,4]oxadiazol-2-yl}-phenoxy)-propyl]-dimethyl-amine (280 mg, 56%) as a yellowish solid.

¹H NMR (CDCl₃) δ 7.93 (d, 2H, J=8.85 Hz), 7.24 (t, 1H, J=8.14 Hz), 6.97 (d, 2H, J=8.85 Hz), 6.79 (d, 2H, J=8.14 Hz), 6.72 (s, 1H), 4.16 (t, 2H, J=6.02 Hz), 4.07 (t, 2H, J=6.37 Hz), 4.00 (s, 2H), 3.03 (t, 2H, J=6.02 Hz), 2.45 (t, 2H, J=7.08 Hz), 2.25 (s, 6H), 1.97 (m, 2H, J=6.37, 7.08 Hz). MS (ES⁺) m/e 498. mp 46.0-46.5 °C. Anal. Calcd for C₂₃H₂₆F₃N₃O₄S: C, 55.52; H, 5.27; N, 8.45; S, 6.44; F, 11.46. Found C, 55.55; H, 5.18; N, 8.32; S, 6.49; F, 11.66.

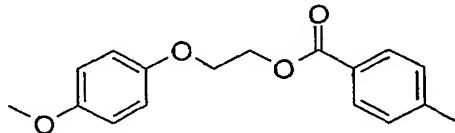
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Example 277

Preparation of [3-(4-{5-[2-(4-methoxy-phenoxy)-ethylsulfanyl methyl]-[1,3,4]oxadiazol-2-yl}-phenoxy)-propyl]-dimethyl-amine



a) 2-(4-Methoxy-phenoxy)-ethyl *p*-toluate

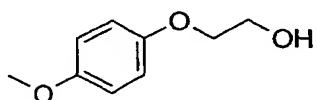


15

In a similar manner as exemplified in Example 274 part d), 4-methoxy-phenol (1.30 g, 10.5 mmol) was converted into 2-(4-methoxy-phenoxy)-ethyl *p*-toluate (2.74 g, 91%) as a white solid.

¹H NMR (CDCl₃) δ 7.92 (d, 2H, J=8.14 Hz), 7.21 (d, 2H, J=8.14 Hz), 6.87 (d, 2H, J=9.20 Hz), 6.81 (d, 2H, J=9.20 Hz), 4.60 (t, 2H, J=4.95 Hz), 4.23 (t, 2H, J=4.95 Hz), 3.75 (s, 3H), 2.38 (s, 3H). MS (ES⁺) m/e 287. mp 40.5-42.5 °C.

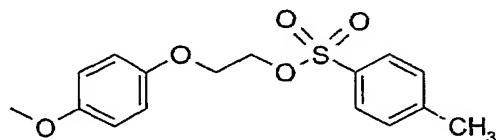
b) 2-(4-Methoxy-phenoxy)-ethanol-1



In a similar manner as exemplified in Example 274 part e), 2-(4-methoxy-phenoxy)-ethyl *p*-toluate (2.29 g, 8 mmol) was converted into 2-(4-methoxy-phenoxy)-ethanol-1 (1.28 g, 95%) as a white solid.

¹H NMR (CDCl₃) δ 6.83 (m, 4H), 4.01 (m, 2H), 3.91 (m, 2H), 3.75 (s, 3H), 2.07 (s, b, 1H). MS (ES⁺) m/e 169. mp 68.5-69.0 °C.

c) 2-(4-Methoxy-phenoxy)-ethyl tosylate

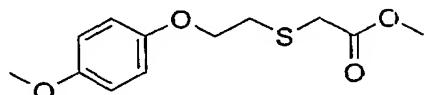


In a similar manner as exemplified in Example 274 part f), 2-(4-methoxy-phenoxy)-ethanol-1 (504 mg, 2 mmol) was converted into 2-(4-methoxy-phenoxy)-ethyl tosylate (245 mg, 25%) as a white solid.

¹H NMR (CDCl₃) δ 7.79 (d, 2H, J=8.14 Hz), 7.31 (d, 2H, J=8.14 Hz), 6.68-6.79 (m, 4H), 4.29-4.34 (m, 2H), 4.05-4.11 (m, 2H), 3.73 (s, 3H), 2.42 (s, 3H). MS (ES⁺) m/e 323. mp 87.0-88.0 °C.

15

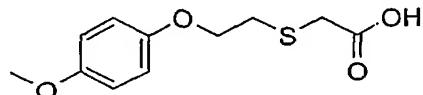
d) Methyl 2-(4-Methoxy-phenoxy)-ethylsulfanyl-acetate



In a similar manner as exemplified in Example 274 part g), 2-(4-methoxy-phenoxy)-ethyl tosylate (245 mg, 0.76 mmol) was converted into methyl 2-(4-methoxy-phenoxy)-ethylsulfanyl-acetate (191 mg, 98%) as a colorless oil.

¹H NMR (CDCl₃) δ 6.81 (m, 4H), 4.11 (t, 2H, J=6.37 Hz), 3.74 (s, 3H), 3.71 (s, 3H), 3.34 (s, 2H), 2.98 (t, 2H, J=6.37 Hz). MS (ES⁺) m/e 257.

e) 2-(4-Methoxy-phenoxy)-ethylsulfanyl acetic acid



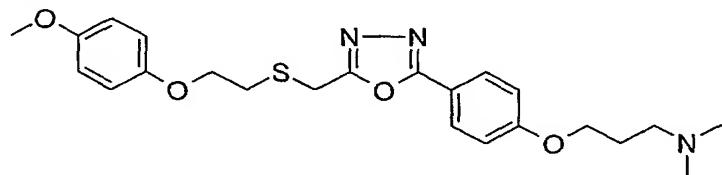
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In a similar manner as exemplified in Example 274 part h), methyl 2-(4-methoxy-phenoxy)-ethylsulfanyl-acetate (191 mg, 0.76 mmol) was converted into 2-(4-methoxy-phenoxy)-ethylsulfanyl acetic acid (144 mg, 79%) as a white solid.

5 ^1H NMR (CDCl_3) δ 6.81 (s, 4H), 4.14 (t, 2H, $J=6.01$ Hz), 3.74 (s, 3H), 3.39 (s, 2H), 3.01 (t, 2H, $J=6.01$ Hz). MS (ES $^-$) m/e 241. mp 68.5-69.0 °C.

f) [3-(4-{5-[2-(4-Methoxy-phenoxy)-ethylsulfanylmethyl]-[1,3,4]oxadiazol-2-yl}-phenoxy)-propyl]-dimethyl-amine



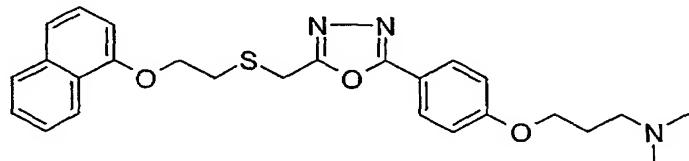
10 In a similar manner as exemplified in Example 274 part i), 2-(4-methoxy-phenoxy)-ethylsulfanyl acetic acid (121 mg, 0.5 mmol) was converted into [3-(4-{5-[2-(4-methoxy-phenoxy)-ethylsulfanylmethyl]-[1,3,4]oxadiazol-2-yl}-phenoxy)-propyl]-dimethyl-amine (85 mg, 39%) as a white solid.

15 ^1H NMR (CDCl_3) δ 7.92 (d, 2H, $J=8.85$ Hz), 6.97 (d, 2H, $J=8.85$ Hz), 6.75-6.84 (m, 4H), 4.12 (t, 2H, $J=6.19$ Hz), 4.07 (t, 2H, $J=6.37$ Hz), 4.00 (s, 2H), 3.73 (s, 3H), 3.00 (t, 2H, $J=6.19$ Hz), 2.45 (t, 2H, $J=7.25$ Hz), 2.25 (s, 6H), 1.97 (m, 2H, $J=6.37, 7.25$ Hz). MS (ES $^+$) m/e 444. mp 77.5-78.0 °C. Anal. Calcd for $\text{C}_{23}\text{H}_{29}\text{N}_3\text{O}_4\text{S}$: C, 62.28; H, 6.59; N, 9.47; S, 7.23. Found C, 62.01; H, 6.60; N, 9.35; S, 7.26.

20

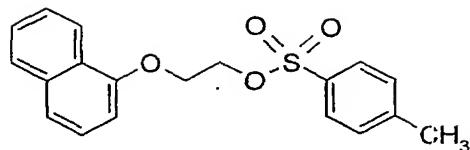
Example 278

Preparation of [3-(4-{5-[2-(1-naphthoxy)-ethylsulfanylmethyl]-[1,3,4]oxadiazol-2-yl}-phenoxy)-propyl]-dimethyl-amine



a) 2-(1-Naphthoxy)-ethyl tosylate

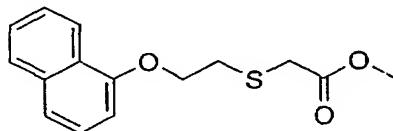
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In a similar manner as exemplified in Example 274 part f), 2-(1-naphthoxy)-ethanol-1 (565 mg, 2 mmol) was converted into 2-(1-naphthoxy)-ethyl tosylate (757 mg, 74%) as a white solid.

5 ¹H NMR (CDCl₃) δ 7.81 (d, 2H, J=8.49 Hz), 7.73 (d, 1H, J=8.14 Hz), 7.69 (d, 1H, J=9.91 Hz), 7.67 (t, 1H, J=8.32 Hz), 7.41 (t, 1H, J=8.14 Hz), 7.33 (d, 1H, J=8.14), 7.30 (d, 2H, J=7.78 Hz), 6.97-7.02 (m, 2H), 4.40-4.44 (m, 2H), 4.22-4.28 (m, 2H), 2.40 (s, 3H). MS (ES⁺) m/e 343. mp 93.0-94.0 °C.

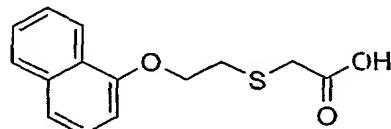
10 b) Methyl 2-(1-naphthoxy)-ethylsulfanyl-acetate



In a similar manner as exemplified in Example 274 part g), 2-(1-naphthoxy)-ethyl tosylate (685 mg, 2 mmol) was converted into methyl 2-(1-naphthoxy)-ethylsulfanyl-acetate (552 mg, 100%) as a colorless oil.

15 ¹H NMR (CDCl₃) δ 8.21-8.27 (m, 1H), 7.74-7.81 (m, 1H), 7.39-7.51 (m, 3H), 7.34 (t, 1H, J=7.79 Hz), 6.79 (t, 1H, J=7.08 Hz), 4.36 (t, 2H, J=6.37 Hz), 3.71 (s, 3H), 3.39 (s, 2H), 3.17 (t, 2H, J=6.37 Hz). MS (ES⁺) m/e 277.

20 c) 2-(1-Naphthoxy)-ethylsulfanyl acetic acid

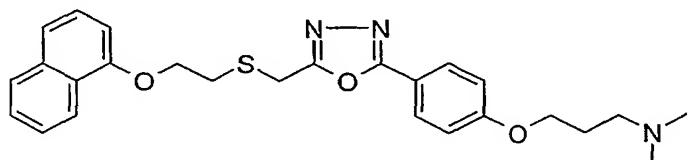


In a similar manner as exemplified in Example 274 part h), methyl 2-(1-naphthoxy)-ethylsulfanyl-acetate (552 mg, 2 mmol) was converted into 2-(1-naphthoxy)-ethylsulfanyl acetic acid (500 mg, 95%) as a white solid.

25 ¹H NMR (CDCl₃) δ 8.20-8.28 (m, 1H), 7.74-7.82 (m, 1H), 7.44-7.50 (m, 2H), 7.42 (d, 1H, J=8.49 Hz), 7.84 (dd, 1H, J=7.78, 8.49 Hz), 6.79 (d, 1H, J=7.78 Hz), 4.37 (t,

2H, J=6.01 Hz), 3.42 (s, 2H), 3.20 (t, 2H, J=6.01 Hz). MS (ES⁻) m/e 261. mp 64.5-65.5 °C.

d) [3-(4-{5-[2-(1-Naphthoxy)-ethylsulfanylmethyl]-[1,3,4]oxadiazol-2-yl}-phenoxy)-propyl]-dimethyl-amine

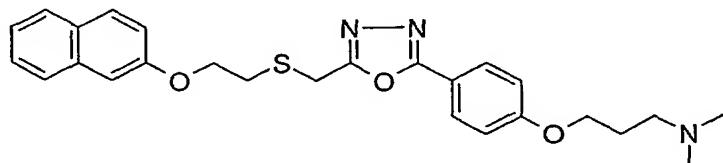


In a similar manner as exemplified in Example 274 part i), 2-(1-naphthoxy)-ethylsulfanyl acetic acid (262 mg, 1 mmol) was converted into [3-(4-{5-[2-(1-naphthoxy)-ethylsulfanylmethyl]-[1,3,4]oxadiazol-2-yl}-phenoxy)-propyl]-dimethyl-amine (344 mg, 74%) as a white solid.

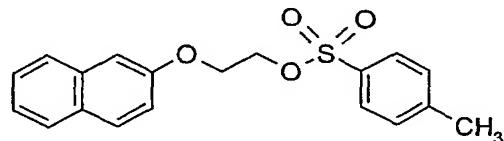
¹H NMR (CDCl₃) δ 8.23-8.28 (m, 1H), 7.88-7.95 (m, 2H), 7.73-7.78 (m, 1H), 7.38-7.49 (m, 3H), 7.33 (t, 1H, J=8.02 Hz), 6.92-6.98 (m, 2H), 6.78 (d, 1H, J=7.43 Hz), 4.37 (t, 2H, J=6.01 Hz), 4.06 (t, 2H, J=6.37 Hz), 4.05 (s, 2H), 3.18 (t, 2H, J=6.01 Hz), 2.46 (t, 2H, J=7.80 Hz), 2.25 (s, 6H), 1.97 (m, 2H, J=6.37, 7.80 Hz). MS (ES⁺) m/e 464. mp 101.0-102.0 °C. Anal. Calcd for C₂₆H₂₉N₃O₃S: C, 67.36; H, 6.31; N, 9.06; S, 6.92. Found C, 67.07; H, 6.23; N, 8.98; S, 6.61.

Example 279

Preparation of [3-(4-{5-[2-(2-naphthoxy)-ethylsulfanylmethyl]-[1,3,4]oxadiazol-2-yl}-phenoxy)-propyl]-dimethyl-amine



a) 2-(2-Naphthoxy)-ethyl tosylate

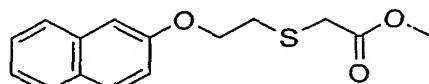


-500-

In a similar manner as exemplified in Example 274 part f), 2-(2-naphthoxy)-ethanol-1 (565 mg, 2 mmol) was converted into 2-(2-naphthoxy)-ethyl tosylate (646 mg, 63%) as a white solid.

¹H NMR (CDCl₃) δ 8.01 (d, 1H, J=8.85 Hz), 7.80 (d, 2H, J=8.49 Hz), 7.76 (d, 1H, J=7.78 Hz), 7.46 (t, 1H, J=8.14 Hz), 7.40 (t, 2H, J=8.49 Hz), 7.29 (t, 1H, J=7.78 Hz), 7.24-7.28 (m, 2H), 6.67 (d, 1H, J=7.43 Hz), 4.50 (t, 2H, J=4.60 Hz), 4.31 (t, 2H, J=4.60 Hz), 2.39 (s, 3H). MS (ES⁺) m/e 343. mp 79.0-80.0 °C.

b) Methyl 2-(2-naphthoxy)-ethylsulfanyl acetate

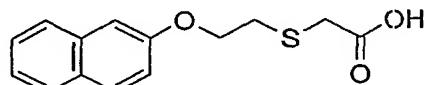


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In a similar manner as exemplified in Example 274 part g), 2-(2-naphthoxy)-ethyl tosylate (514 mg, 1.5 mmol) was converted into methyl 2-(1-naphthoxy)-ethylsulfanyl-acetate (414 mg, 100%) as a colorless oil.

¹H NMR (CDCl₃) δ 7.68-7.76 (m, 3H), 7.42 (q, 1H, J=6.72, 8.14 Hz), 7.32 (q, 1H, J=6.72, 7.08 Hz), 7.12 (d, 1H, J=8.14 Hz), 7.11 (s, 1H), 4.29 (t, 2H, J=6.37 Hz), 3.72 (s, 3H), 3.38 (s, 2H), 3.08 (t, 2H, J=6.37 Hz). MS (ES⁺) m/e 277.

c) 2-(2-Naphthoxy)-ethylsulfanyl acetic acid



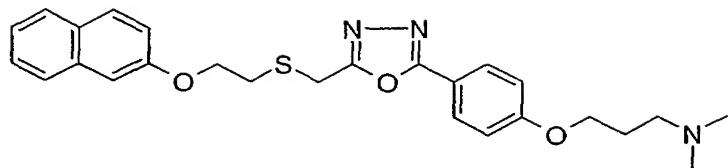
20

In a similar manner as exemplified in Example 274 part h), methyl 2-(2-naphthoxy)-ethylsulfanyl-acetate (414 mg, 1.5 mmol) was converted into 2-(2-naphthoxy)-ethylsulfanyl acetic acid (345 mg, 88%) as a white solid.

¹H NMR (CDCl₃) δ 7.66-7.77 (m, 3H), 7.42 (t, 1H, J=8.14 Hz), 7.32 (t, 1H, J=8.14 Hz), 7.08-7.15 (m, 2H), 4.30 (t, 2H, J=6.01 Hz), 3.38 (s, 2H), 3.08 (t, 2H, J=6.01 Hz). MS (ES⁻) m/e 261. mp 99.5-100.5 °C.

d) [3-(4-{5-[2-(2-Naphthoxy)-ethylsulfanyl]methyl}-[1,3,4]oxadiazol-2-yl}-phenoxy]-propyl]-dimethyl-amine

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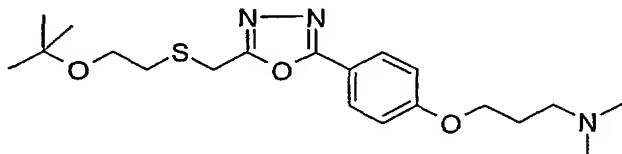


In a similar manner as exemplified in Example 274 part i), 2-(2-naphthoxy)-ethylsulfanyl acetic acid (262 mg, 1 mmol) was converted into [3-(4-{5-[2-(2-naphthoxy)-ethylsulfanylmethyl]-[1,3,4]oxadiazol-2-yl}-phenoxy)-propyl]-dimethyl-amine (291 mg, 63%) as a white solid.

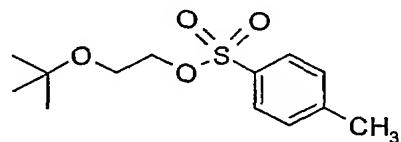
¹H NMR (CDCl₃) δ 7.89 (d, 2H, J=8.85 Hz), 7.73 (d, 1H, J=8.14 Hz), 7.69 (t, 2H, J=8.14 Hz), 7.41 (q, 1H, J=7.08, 7.78 Hz), 7.31 (q, 1H, J=6.72, 7.08 Hz), 7.09-7.14 (m, 2H), 6.91 (d, 2H, J=8.85 Hz), 4.30 (t, 2H, J=6.01 Hz), 4.05 (s, 2H), 4.04 (t, 2H, J=6.37 Hz), 3.10 (t, 2H, J=6.01 Hz), 2.44 (t, 2H, J=7.16 Hz), 2.24 (s, 6H), 1.96 (m, 2H, J=6.37, 7.16 Hz). MS (ES⁺) m/e 464. mp 97.0-98.0 °C. Anal. Calcd for C₂₆H₂₉N₃O₃S: C, 67.36; H, 6.31; N, 9.06; S, 6.92. Found C, 66.89; H, 6.41; N, 8.95; S, 6.89.

Example 280

Preparation of (3-{4-[5-(2-*tert*-butoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine



a) 2-*tert*-Butoxy-ethyl tosylate

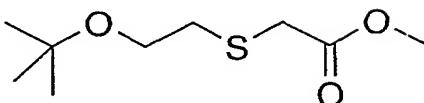


In a similar manner as exemplified in Example 274 part f), 2-*tert*-butoxy-ethanol-1 (2.36 g, 20 mmol) was converted into 2-*tert*-butoxy-ethyl tosylate (5.21 g, 96%) as a colorless oil.

¹H NMR (CDCl₃) δ 7.78 (d, 2H, J=8.14 Hz), 7.31 (d, 2H, J=8.14 Hz), 4.09 (t, 2H, J=5.13 Hz), 3.52 (t, 2H, J=5.13 Hz), 2.42 (s, 3H), 1.10 (s, 9H). MS (ES⁺) m/e 273.

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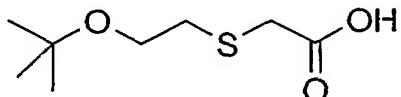
b) Methyl 2-(2-*tert*-butoxy)-ethylsulfanyl-acetate



In a similar manner as exemplified in Example 274 part g), 2-*tert*-butoxy-ethyl tosylate (5.21 g, 19 mmol) was converted into methyl 2-*tert*-butoxy-ethylsulfanyl-acetate (3.94 g, 100%) as a colorless oil.

¹H NMR (CDCl₃) δ 3.71 (s, 3H), 3.54 (t, 2H, J=6.55 Hz), 3.30 (s, 2H), 2.75 (t, 2H, J=6.55 Hz), 1.17 (s, 9H). MS (ES⁺) m/e 207.

c) 2-*tert*-Butoxy-ethylsulfanyl acetic acid

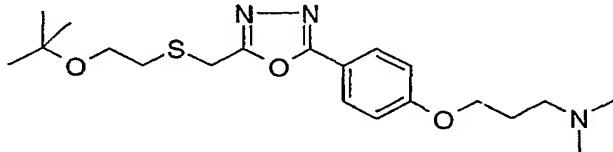


10

In a similar manner as exemplified in Example 274 part h), methyl 2-(2-*tert*-butoxy)-ethylsulfanyl-acetate (3.94 g, 19 mmol) was converted into 2-*tert*-butoxy-ethylsulfanyl acetic acid (3.30 g, 90%) as a colorless oil.

¹H NMR (CDCl₃) δ 3.63 (t, 2H, J=6.01 Hz), 3.35 (s, 2H), 2.80 (t, 2H, J=6.01 Hz), 1.20 (s, 9H). MS (ES⁺) m/e 191.

d) (3-{4-[5-(2-*tert*-Butoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine



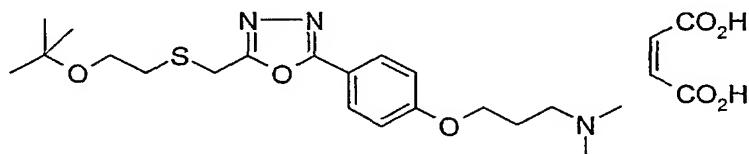
20

In a similar manner as exemplified in Example 274 part i), 2-*tert*-butoxy-ethylsulfanyl acetic acid (777 mg, 4 mmol) was converted into (3-{4-[5-(2-*tert*-Butoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine (590 mg, 37%) as a brown oil.

¹H NMR (CDCl₃) δ 7.95 (d, 2H, J=8.85 Hz), 6.97 (d, 2H, J=8.85 Hz), 4.06 (t, 2H, J=6.37 Hz), 3.97 (s, 2H), 3.55 (t, 2H, J=6.29 Hz), 2.78 (t, 2H, J=6.29 Hz), 2.44 (t, 2H, J=7.26 Hz), 2.24 (s, 6H), 1.96 (m, 2H, J=6.37, 7.26 Hz), 1.16 (s, 9H). MS (ES⁺) m/e 394.

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e) (3-{4-[5-(2-*tert*-Butoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine maleate

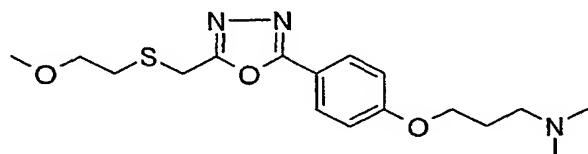


5 To a hot solution of maleic acid (193 mg, 1.7 mmol) in ethyl acetate (1 mL) was added a solution of (3-{4-[5-(2-*tert*-Butoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine (590 mg, 1.5 mmol) in ethyl acetate with stirring. After 10 minutes, solvent was removed on a rotary evaporator. The oily residue was dissolved in dichloromethane (1 mL) followed by addition of diethyl ether (20 mL). The 10 mixture was rapidly stirred at 23 °C till solid formed. The solid was collected by filtration, washed with diethyl ether (3 × 5 mL), and dried in vacuum to provide a light brown solid (300 mg, 39%).

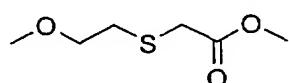
15 ^1H NMR (CDCl_3) δ 7.96 (d, 2H, $J=8.85$ Hz), 6.94 (d, 2H, $J=8.85$ Hz), 6.22 (s, 2H), 4.13 (t, 2H, $J=5.48$ Hz), 3.97 (s, 2H), 3.56 (t, 2H, $J=6.19$ Hz), 3.27 (t, 2H, $J=7.96$ Hz), 2.87 (s, 6H), 2.77 (t, 2H, $J=6.19$ Hz), 2.22-2.34 (m, 2H), 1.16 (s, 9H). MS (ES^+) m/e 394. mp 84.5-85.5 °C. Anal. Calcd for $\text{C}_{24}\text{H}_{35}\text{N}_3\text{O}_7\text{S}$: C, 56.56; H, 6.92; N, 8.25; S, 6.29. Found C, 56.33; H, 6.85; N, 8.36; S, 6.03.

Example 281

20 Preparation of (3-{4-[5-(2-methoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine



a) Methyl 2-(2-methoxy)-ethylsulfanyl-acetate

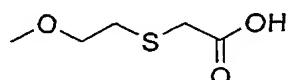


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In a similar manner as exemplified in Example 274 part g), 2-bromoethyl methyl ether (1.39 g, 10 mmol) was converted into methyl 2-(2-methoxy)-ethylsulfanyl-acetate (1.06 g, 64%) as a colorless oil.

5 ^1H NMR (CDCl_3) δ 3.71 (s, 3H), 3.57 (t, 2H, $J=6.37$ Hz), 3.33 (s, 3H), 3.27 (s, 2H), 2.80 (t, 2H, $J=6.37$ Hz). MS (ES^+) m/e 165.

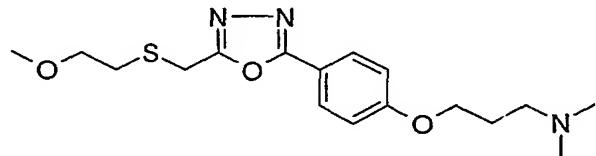
b) 2-Methoxy-ethylsulfanyl acetic acid



10 In a similar manner as exemplified in Example 274 part h), methyl 2-(2-methoxy)-ethylsulfanyl-acetate (1.06 g, 19 mmol) was converted into 2-methoxy-ethylsulfanyl acetic acid (0.84 g, 87%) as a colorless oil.

15 ^1H NMR (CDCl_3) δ 3.62 (t, 2H, $J=6.01$ Hz), 3.36 (s, 3H), 3.32 (s, 2H), 2.84 (t, 2H, $J=6.01$ Hz). MS (ES^-) m/e 149.

20 c) (3-{4-[5-(2-Methoxy-ethylsulfanyl)methyl]-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine



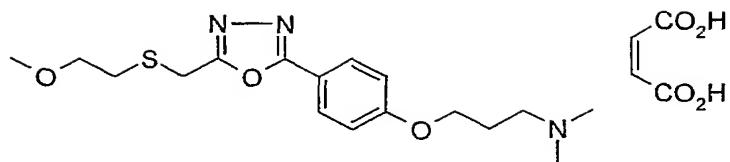
25 In a similar manner as exemplified in Example 274 part i), 2-methoxy-ethylsulfanyl acetic acid (549 mg, 3.7 mmol) was converted into (3-{4-[5-(2-methoxy-ethylsulfanyl)methyl]-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine (900 mg, 69%) as a white solid.

20 ^1H NMR (CDCl_3) δ 7.96 (d, 2H, $J=8.85$ Hz), 6.95 (d, 2H, $J=8.85$ Hz), 4.15 (t, 2H, $J=5.66$ Hz), 3.94 (s, 2H), 3.58 (t, 2H, $J=6.01$ Hz), 3.32 (s, 3H), 3.19-3.26 (m, 2H), 2.83 (s, 6H), 2.81 (m, 2H, $J=6.01$ Hz), 2.37-2.46 (m, 2H). MS (ES^+) m/e 352.

25

d) (3-{4-[5-(2-Methoxy-ethylsulfanyl)methyl]-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine maleate

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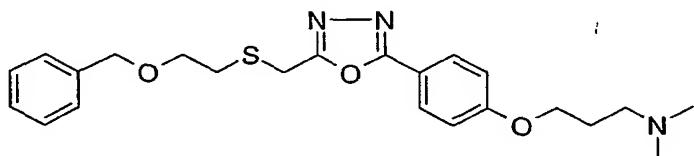


In a similar manner as exemplified in Example 280 part e), (3-{4-[5-(2-methoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine (300 mg, 0.85 mmol) was converted (3-{4-[5-(2-methoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine maleate (278 mg, 70%) as a white solid.

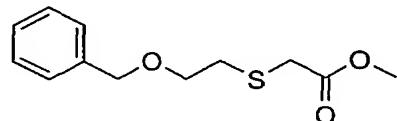
¹H NMR (CDCl_3) δ 7.97 (d, 2H, $J=8.85$ Hz), 6.95 (d, 2H, $J=8.85$ Hz), 6.23 (s, 2H), 4.13 (t, 2H, $J=5.66$ Hz), 3.95 (s, 2H), 3.59 (t, 2H, $J=6.01$ Hz), 3.33 (s, 3H), 3.26 (t, 2H, $J=7.96$ Hz), 2.86 (s, 6H), 2.82 (t, 2H, $J=6.01$ Hz), 2.24-2.84 (m, 2H). MS (ES^+) m/e 352. mp 97.5-99.0 °C. Anal. Calcd for $\text{C}_{21}\text{H}_{29}\text{N}_3\text{O}_7\text{S}$: C, 53.95; H, 6.25; N, 8.99; S, 6.86. Found C, 53.83; H, 6.26; N, 8.92; S, 6.99.

Example 282

Preparation of (3-{4-[5-(2-phenylmethoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine



a) Methyl 2-(2-phenylmethoxy)-ethylsulfanyl-acetate

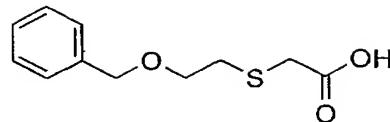


In a similar manner as exemplified in Example 274 part g), benzyl 2-bromoethyl ether (2.15 g, 10 mmol) was converted into methyl 2-(2-phenylmethoxy)-ethylsulfanyl-acetate (2.19 g, 91%) as a colorless oil.

¹H NMR (CDCl_3) δ 7.21-7.39 (m, 5H), 4.52 (s, 2H), 3.69 (s, 3H), 3.66 (t, 2H, $J=6.37$ Hz), 3.28 (s, 2H), 2.85 (t, 2H, $J=6.37$ Hz). MS (ES^+) m/e 241.

b) 2-Phenylmethoxy-ethylsulfanyl acetic acid

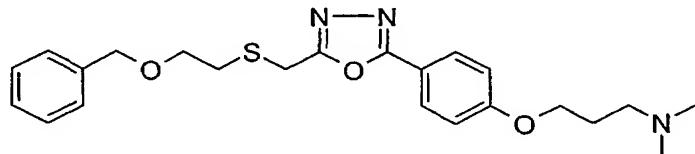
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In a similar manner as exemplified in Example 274 part h), methyl 2-(2-phenylmethoxy)-ethylsulfanyl-acetate (2.16 g, 9 mmol) was converted into 2-phenylmethoxy-ethylsulfanyl acetic acid (1.89 g, 92%) as a colorless oil.

5 ^1H NMR (CDCl_3) δ 7.23-7.36 (m, 5H), 4.53 (s, 2H), 3.69 (t, 2H, $J=6.19$ Hz), 3.32 (s, 2H), 2.87 (t, 2H, $J=6.19$ Hz). MS (ES $^-$) m/e 225.

c) (3-{4-[5-(2-Phenylmethoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine

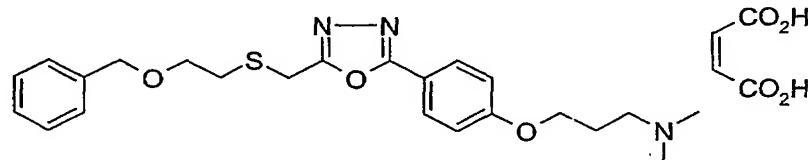


10

In a similar manner as exemplified in Example 274 part i), 2-phenylmethoxy-ethylsulfanyl acetic acid (675 mg, 3 mmol) was converted into (3-{4-[5-(2-phenylmethoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine (994 mg, 78%) as a white solid.

15 ^1H NMR (CDCl_3) δ 7.93 (d, 2H, $J=8.85$ Hz), 7.21-7.34 (m, 5H), 6.97 (d, 2H, $J=8.85$ Hz), 4.52 (s, 2H), 4.06 (t, 2H, $J=6.37$ Hz), 3.94 (s, 2H), 3.67 (t, 2H, $J=6.37$ Hz), 2.86 (t, 2H, $J=6.37$ Hz), 2.44 (t, 2H, $J=7.26$ Hz), 2.24 (s, 6H), 1.96 (m, 2H, $J=6.37, 7.26$ Hz). MS (ES $^+$) m/e 428.

20 d) (3-{4-[5-(2-Phenylmethoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine maleate



In a similar manner as exemplified in Example 280 part e), (3-{4-[5-(2-phenylmethoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-

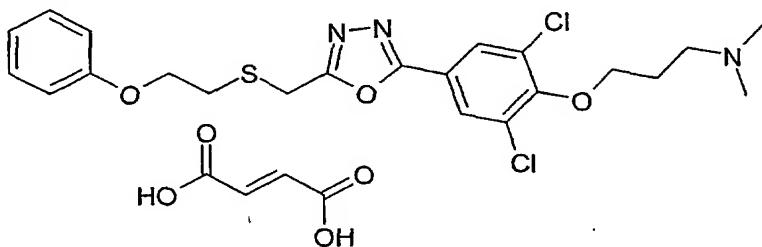
amine (497 mg, 1.16 mmol) was converted (3-{4-[5-(2-phenylmethoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine maleate (537 mg, 85%) as a white solid.

¹H NMR (CDCl₃) δ 7.95 (d, 2H, J=8.85 Hz), 7.20-7.34 (m, 5H), 6.94 (d, 2H, J=8.85 Hz), 6.25 (s, 2H), 4.52 (s, 2H), 4.13 (t, 2H, J=5.48 Hz), 3.95 (s, 2H), 3.68 (t, 2H, J=6.37 Hz), 3.27 (t, 2H, J=7.96 Hz), 2.87 (s, 6H), 2.86 (t, 2H, J=6.37 Hz), 2.30 (m, 2H, J=5.48, 7.96 Hz). MS (ES⁺) m/e 428. mp 71.5-72.0 °C. Anal. Calcd for C₂₇H₃₃N₃O₇S: C, 59.65; H, 6.12; N, 7.73; S, 5.90. Found C, 59.52; H, 6.07; N, 7.73; S, 5.99.

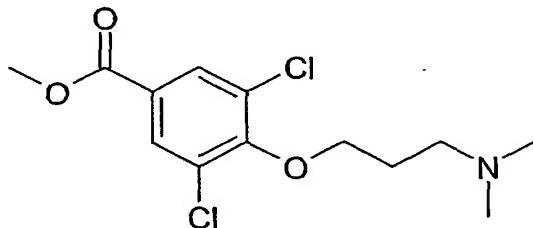
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Example 283

Preparation of (3-{2,6-dichloro-4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine; fumaric acid salt



a) Methyl 3,5-dichloro-4-(3-dimethylamino-propoxy)-benzoate



15

17.05 gm (77.1 mmol) of methyl 3,5-dichloro-4-hydroxybenzoate, 22.26 gm (84.9 mmol) of triphenylphosphine, and 10.0 mL (84.9 mmol) of 3-dimethylaminopropan-1-ol were dissolved in 100 mL of dry THF and with stirring under dry nitrogen cooled to 0 °C.

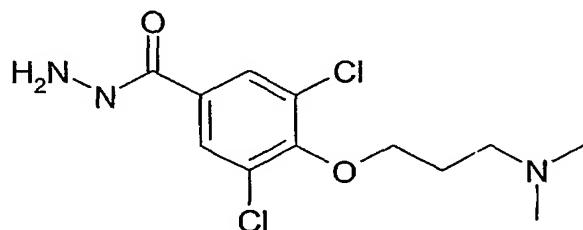
16.7 ml (84.9 mmol) of diisopropylazodicarboxylate was then slowly added over 5 minutes. Stirring was continued at 0 °C for 2 hours and then at room temperature for a further 2 hours. The solvents were then removed under reduced pressure to yield an oil. This was diluted with about 100 mL of ethylacetate which was then extracted 3 times with 3N HCl. The aqueous extracts were combined, cooled to 0 °C and solid sodium hydroxide was added until the aqueous phase was at least pH 10. The basified aqueous

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fraction was then extracted twice with 50 ml portions of methylene chloride which were then combined, dried over magnesium sulfate, filtered, and evaporated to give 16.3 gm (70%) of methyl 3,5-dichloro-4-(3-dimethylamino-propoxy)-benzoate as a thick syrup.

- 5 ^1H NMR ($\text{CHCl}_3\text{-d}1$) δ 7.91 (s, 1H), 4.09 (t, 2H, $J = 6.37$ Hz), 3.86 (s, 3H), 2.49 (t, 2H, $J = 7.78$ Hz), 2.22 (s, 6H), 1.95 - 2.02 (m, 2H).

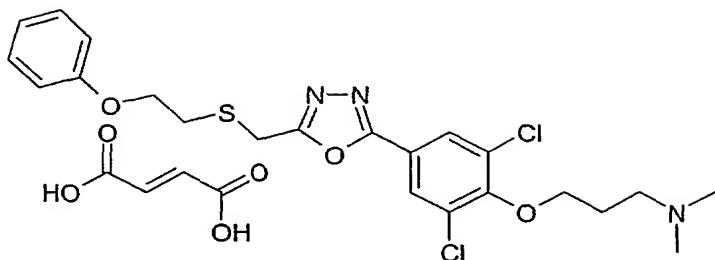
b) 3,5-Dichloro-4-(3-dimethylamino-propoxy)-benzoic acid hydrazide



- 10 5.01 gm (16.43 mmol) of methyl 3,5-dichloro-4-(3-dimethylamino-propoxy)-benzoate was dissolved in 15 mL of ethanol and 15 ml of hydrazine hydrate were added. The mixture was heated at 90 °C for 5.5h and then cooled to room temperature. The mixture was diluted with about 100 mL of methylene chloride, which was then washed with about 30 mL of water. The aqueous layer was washed once with about 30 ml of ethylacetate
 15 and then the organic fractions were combined, dried over magnesium sulfate, filtered, and evaporated to yield 3.56 gm (71%) of 3,5-dichloro-4-(3-dimethylamino-propoxy)-benzoic acid hydrazide as a waxy solid.

- 19 ^1H NMR ($\text{CHCl}_3\text{-d}1$) δ 7.69 (s, 2H), 4.08 (t, 2H, $J = 6.72$ Hz), 2.50 (t, 2H, $J = 7.78$ Hz),
 20 2.23 (s, 6H), 1.95 – 2.02 (m, 2H).

c) (3-{2,6-Dichloro-4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine; fumaric acid salt



3.05 gm (10.0 mmol) of 3,5-dichloro-4-(3-dimethylamino-propoxy)-benzoic acid hydrazide, 2.12 gm (10.0 mmol) of (2-phenoxy-ethylsulfanyl)-acetic acid, 7.87 gm (30.0 mmol) of triphenylphosphine, 8.3 ml (60.0 mmol) of triethylamine, were suspended in 25 mL of dry acetonitrile and stirred at room temperature. 4.8 mL (50.0 mmol) of carbon tetrachloride was then slowly added. The resultant mixture was stirred at room temperature for about 5 hours and then the solvent was removed under reduced pressure. The resultant oil was diluted with about 50 mL of ethylacetate which was then extracted with two portions of about 15 mL 3N HCl. The combined acidic extracts were basified with solid sodium hydroxide and then extracted with two approximately 30 mL portions of methylene chloride. The methylene chloride extracts were dried over magnesium sulfate, filtered, and then evaporated to yield 3.94 gm of a dark red oil. The oil was chromatographed on about 100 gm of silica gel using sequentially 500 mL of ethylacetate, a 1,000 mL gradient of from 0 to 40% methanol in ethylacetate and then 1,000 mL of 40% methanol in methylene chloride to give 1.45 gm of the desired free base. This was dissolved in a mixture of ethylacetate and methylene chloride and 344 mg of fumaric acid was added. The solvents were evaporated and the residue was triturated in diethyl ether to give 1.48 gm of (3-{2,6-dichloro-4-[5-(2-phenoxy-ethylsulfanyl)methyl]-[1,3,4]oxadiazol-2-yl}-phenoxy)-propyl-dimethyl-amine; fumaric acid salt as a solid. mp = 95 - 99°C.

20

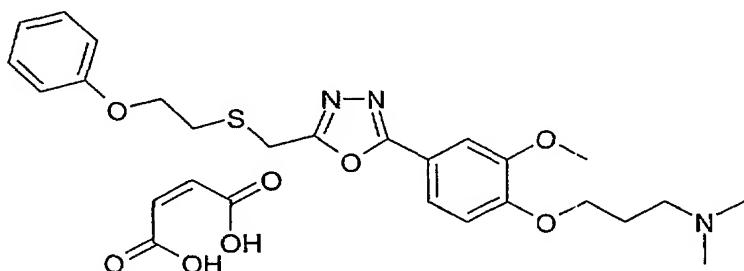
¹H NMR (CH₃OH-d4) δ 7.97 (s, 2H), 7.18 (t, 2H, J = 8.14 Hz), 6.81 – 6.87 (m, 3H), 6.66 (s, 2H), 4.21 (t, 2H, J = 5.66 Hz), 4.13 – 4.17 (m, 4H), 3.40 – 3.46 (m, 2H), 3.03 (t, 2H, J = 6.01 Hz), 2.91 (s, 6H), 2.23 – 2.32 (m, 2H).

25 Anal. Calcd for C₂₆H₂₉Cl₂N₃O₇S: C, 52.18; H, 4.88; N, 7.02; Cl, 11.85. Found C, 52.20; H, 4.74; N, 7.88; Cl, 11.86.

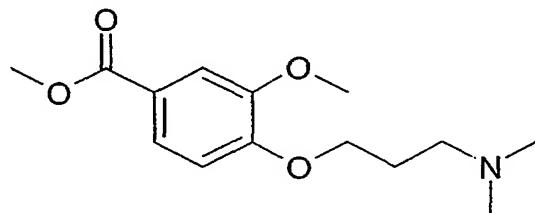
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Example 284

Preparation of (3-{2-methoxy-4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine; maleic acid salt



- 5 a) Methyl 4-(3-dimethylamino-propoxy)-3-methoxy benzoate

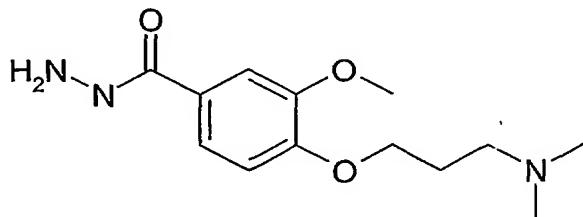


In a similar manner as exemplified in Example 283 part a), 10.0 gm of methyl 4-hydroxy-3-methoxybenzoate was converted into 16.08 gm of methyl 4-(3-dimethylamino-propoxy)-3-methoxy benzoate as a yellow oil.

10

¹H NMR (CHCl₃-d1) δ 7.60 (dd, 1H, J = 8.49, 2.12 Hz), 7.50 (d, 1H, J = 2.12 Hz), 6.86 (d, 1H, J = 8.49 Hz), 4.09 (t, 2H, J = 6.72 Hz), 3.87 (s, 3H), 3.84 (s, 3H), 2.41 (t, 2H, J = 7.08 Hz), 2.20 (s, 6H), 1.94 – 2.04 (m, 2H).

- 15 b) 4-(3-Dimethylamino-propoxy)-3-methoxy benzoic acid hydrazide



In a similar manner as exemplified in Example 283 part b), 16 gm of methyl 4-(3-dimethylamino-propoxy)-3-methoxy benzoate was converted into 4-(3-dimethylamino-propoxy)-3-methoxy benzoic acid hydrazide a portion of which was purified by

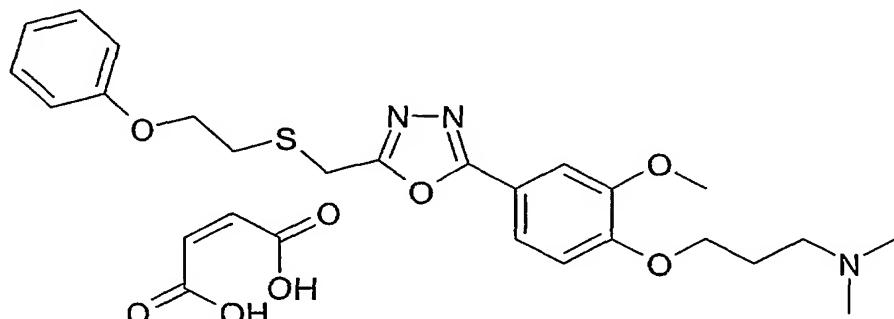
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chromatography on silica gel using a 6% 2N ammonia in methanol mixture in methylene chloride to yield 1.35 gm of a white solid.

5 ^1H NMR ($\text{CHCl}_3\text{-d}1$) δ 8.06 (bs, 1H), 7.83 (d, 1H, $J = 2.12$ Hz), 7.22 (dd, 1H, $J = 8.40$ Hz), 6.80 (d, 1H, $J = 8.49$ Hz), 4.02 (t, 2H, $J = 6.72$ Hz), 3.81 (s, 3H), 2.38 (t, 2H, $J = 7.43$ Hz, 2.17 (s, 6H), 1.90 – 1.99 (m, 2H).

c) (3-{2-Methoxy-4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine; maleic acid salt

10



15

In a similar manner as exemplified in Example 283 part c), 1.37 gm of 4-(3-dimethylamino-propoxy)-3-methoxy benzoic acid hydrazide was converted into 1.62 gm of (3-{2-methoxy-4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine; maleic acid salt except: The initial reaction mixture was evaporated to dryness, taken up in ethyl acetate, and washed with saturated sodium bicarbonate. The organic phase was dried over magnesium sulfate, filtered, and evaporated to yield a solid which was chromatographed on about 100 gm of silica gel using 500 mL of ethylacetate, a 500 mL gradient of a 0 to 5% 2N ammonia in methanol mixture in methylene chloride, and 1,500 mL of a 5% 2N ammonia in methanol mixture in methylene chloride. The free base was converted into the maleic acid salt by addition of an equivalent of maleic acid to the free base in hot ethyl acetate. The desired salt precipitated from solution as a white solid which was collected by filtration. mp = 114 – 116°C.

25

^1H NMR ($\text{CH}_3\text{OH-d}4$) δ 7.54 – 7.58 (m, 2H), 7.19 (t, 2H, $J = 8.14$ Hz), 7.09 (d, 1H, $J = 8.85$ Hz), 6.84 – 6.90 (m, 2H), 6.20 (s, 2H), 4.22 (t, 2H, $J = 5.66$ Hz), 4.17 (t, 2H, $J = 6.01$

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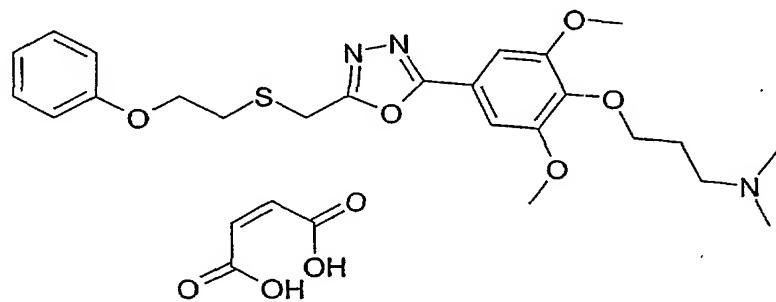
Hz), 4.13 (s, 2H), 3.90 (s, 3H), 3.38 (t, 2H, J = 7.08 Hz), 3.03 (t, 2H, J = 6.01 Hz), 2.96 (s, 6H), 2.23 – 2.31 (m, 2H).

Anal. Calcd for C₂₇H₃₃N₃O₈S: C, 57.95; H, 5.94; N, 7.51. Found C, 58.02; H, 5.89; N,

5 7.49.

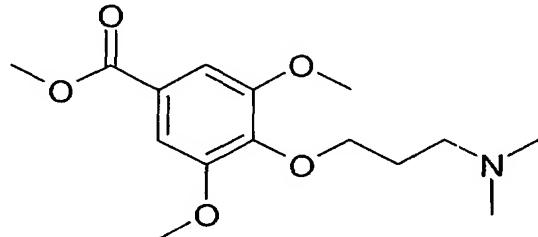
Example 285

Preparation of (3-{2,6-dimethoxy-4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine; maleic acid salt



10

a) Methyl 3,5-dimethoxy-4-(3-dimethylamino-propoxy)-benzoate



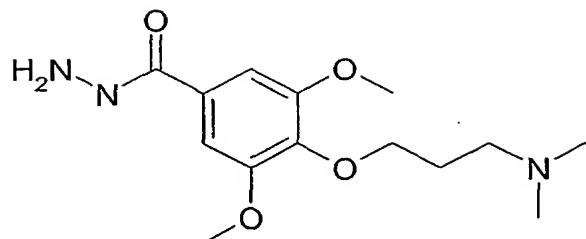
In a similar manner as exemplified for Example 283, part a), 5.0 gm (23.56 mmol) of

15 methyl 3,5-dimethoxy-4-hydroxybenzoate was converted into 6.96 gm (100%) of methyl 3,5-dimethoxy-4-(3-dimethylamino-propoxy)-benzoate as a yellow oil.

¹H NMR (CHCl₃-d1) δ 7.25 (s, 2H), 4.05 (t, 2H, J = 6.72 Hz), 3.86 (s, 3H), 3.85 (s, 6H), 2.44 (t, 2H, J = 7.08 Hz), 2.20 (s, 6H), 1.84 – 1.93 (m, 2H).

20 b) 3,5-dimethoxy-4-(3-dimethylamino-propoxy)-benzoic acid hydrazide

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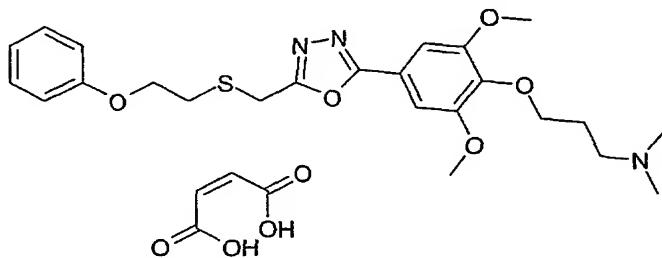


In a similar manner as exemplified for Example 283, part b), 2.49 gm of methyl 3,5-dimethoxy-4-(3-dimethylamino-propoxy)-benzoate was converted into 1.99 gm (80%) of 3,5-dimethoxy-4-(3-dimethylamino-propoxy)-benzoic acid hydrazide as a white waxy solid excepting that the reaction was carried out at room temperature for 24h. mp = 95 - 96°C

¹H NMR (CHCl₃-d1) δ 6.93 (s, 2H), 4.02 (t, 2H, J = 6.72 Hz), 3.84 (s, 6H), 2.44 (t, 2H, J = 7.08 Hz), 2.21 (s, 6H), 1.84 – 1.93 (m, 2H).

10

c) (3-{2,6-Dimethoxy-4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine; maleic acid salt



In a similar manner as exemplified for Example 284 part c), 1.06 gm of 3,5-dimethoxy-4-(3-dimethylamino-propoxy)-benzoic acid hydrazide was converted into 1.20 gm of (3-{2,6-dimethoxy-4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine; maleic acid salt as a white solid except that 2N sodium hydroxide was substituted for the saturated sodium bicarbonate in the ethyl acetate wash. mp = 103 – 104 °C

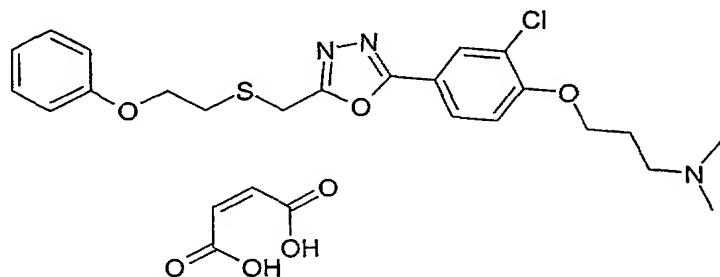
20 ¹H NMR (CH₃OH-d4) δ 7.30 (s, 2H), 7.19 (t, 2H, J = 7.78 Hz), 6.84 – 6.89 (m, 2H), 6.22 (s, 2H), 4.13 – 4.19 (m, 6H), 3.91 (s, 6H), 3.45 (t, 2H, J = 6.72 Hz), 3.04 (t, 2H, J = 6.01 Hz), 2.96 (s, 6H), 2.12 – 2.19 (m, 2H).

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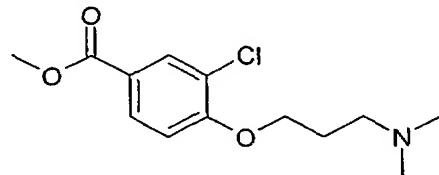
Anal. Calcd for C₂₈H₃₅N₃O₉S: C, 57.03; H, 5.98; N, 7.13. Found C, 57.01; H, 5.84; N, 7.10.

Example 286

- 5 Preparation of (3-{2-chloro-4-[5-(2-phenoxy-ethylsulfanyl-methyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine; maleic acid salt

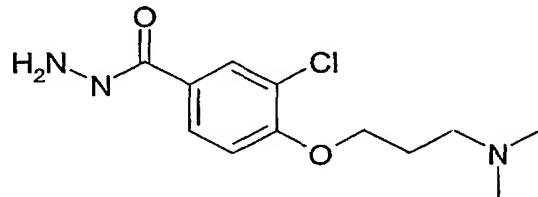


- a) Methyl 3-chloro-4-(3-dimethylamino-propoxy)-benzoate



- 10 In a similar manner as exemplified for Example 283, part a), 5.01 gm of methyl 3-chloro-4hydroxybenzoate was converted into 6.39 gm of methyl 3-chloro-4-(3-dimethylamino-propoxy)-benzoate as a yellow oil.

¹H NMR (CHCl₃-d1) δ 8.00 (d, 1H, J = 2.12 Hz), 7.86 (dd, 1H, J = 8.49, 2.12 Hz), 6.91 (d, 1H, J = 8.85 Hz), 4.11 (t, 2H, J = 6.72 Hz), 3.85 (s, 3H), 2.45 (t, 2H, J = 7.08 Hz), 2.22 (s, 6H), 1.94 – 2.03 (m, 2H).



- b) 3-Chloro-4-(3-dimethylamino-propoxy)-benzoic acid hydrazide

In a similar manner as exemplified for example 285 part b), 6.35 gm of methyl 3-chloro-

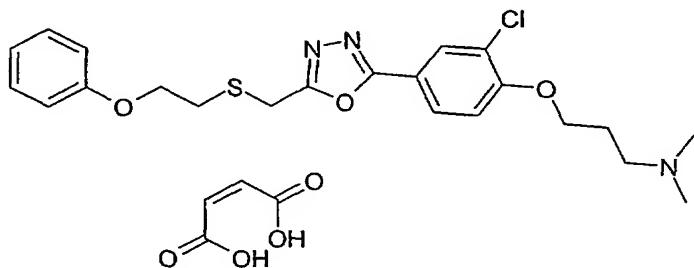
4-(3-dimethylamino-propoxy)-benzoate was converted into 5.81 gm of 3-chloro-4-(3-

- 20 dimethylamino-propoxy)-benzoic acid hydrazide as a white waxy solid.

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¹H NMR (CHCl₃-d1) δ 8.06 (bs, 1H), 7.79 (d, 1H, J = 2.12 Hz), 7.61 (dd, 1H, J = 8.40, 2.48 Hz), 6.88 (d, 1H, J = 8.85 Hz), 4.07 (t, 2H, J = 6.37 Hz), 2.44 (t, 2H, J = 7.08 Hz), 2.21 (s, 6H), 1.92 – 2.01 (m, 2H).

5 c) (3-{2-Chloro-4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine; maleic acid salt



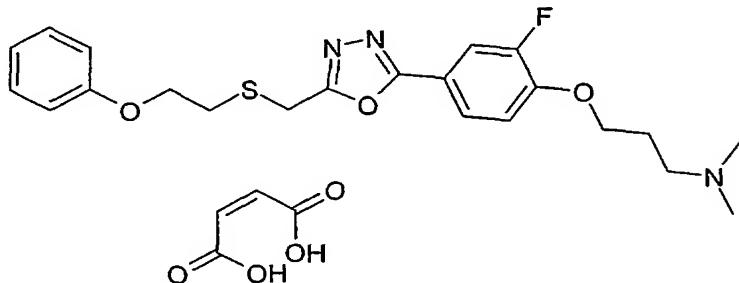
In a similar manner as exemplified for example 284 part c), 2.49 gm of 3-chloro-4-(3-dimethylamino-propoxy)-benzoic acid hydrazide was converted into 1.84 gm of (3-{2-chloro-4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine; maleic acid salt as a white solid.

10 ¹H NMR (CH₃OH-d4) δ 7.99 (d, 1H, J = 2.12 Hz), 7.90 (dd, 1H, J = 8.85, 2.12 Hz), 7.16 – 7.26 (m, 3H), 6.83 – 6.89 (m, 3H), 6.21 (s, 2H), 4.27 (t, 2H, J = 5.66 Hz), 4.17 (t, 2H, J = 6.01 Hz), 4.13 (s, 2H), 3.38 (t, 2H, J = 7.43), 3.03 (t, 2H, J = 6.01 Hz), 2.95 (s, 6H), 2.26 – 2.85 (m, 2H).

15 Anal. Calcd for C₂₆H₃₀ClN₃O₇S: C, 55.36; H, 5.36; N, 7.45; Cl, 6.29. Found C, 55.50; H, 5.24; N, 7.37, Cl, 6.29.

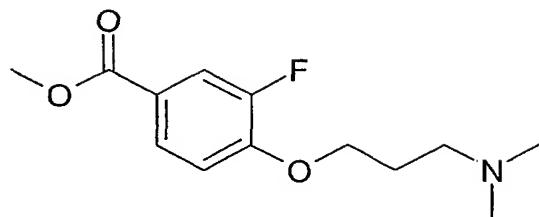
Example 287

Preparation of (3-{2-fluoro-4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine; maleic acid salt



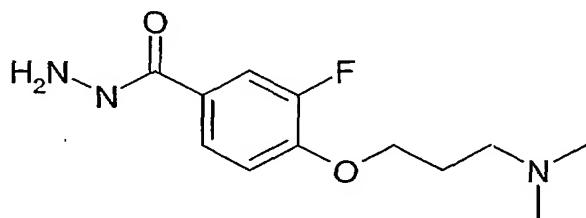
a) Methyl 4-(3-dimethylamino-propoxy)-3-fluoro benzoate

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In a similar manner as exemplified in Example 283 part a), 2.82 gm of methyl 3-fluoro-4-hydroxybenzoate was converted into 3.95 gm of methyl 4-(3-dimethylamino-propoxy)-3-fluoro benzoate as a yellow oil.

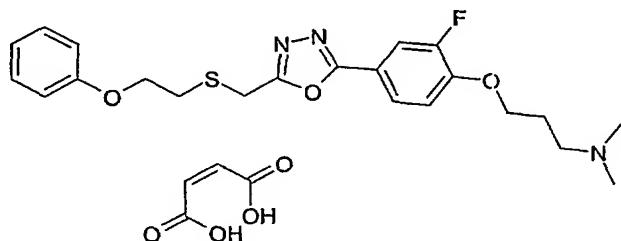
- 5 ^1H NMR ($\text{CHCl}_3\text{-d}1$) δ 7.74 (d, 1H, $J = 9.20$ Hz), 7.69 (d, 1H, $J = 9.55$ Hz), 4.11 (t, 2H, $J = 6.37$ Hz), 3.84 (s, 3H), 2.42 (t, 2H, 6.72 Hz), 2.21 (s, 6H), 1.92 – 2.01 (m, 2H).
- b) 4-(3-Dimethylamino-propoxy)-3-fluoro benzoic acid hydrazide



- 10 In a similar manner as exemplified in Example 285 part b), 3.84 gm of methyl 4-(3-dimethylamino-propoxy)-3-fluoro benzoate was converted into 3.51 gm of 4-(3-dimethylamino-propoxy)-3-fluoro benzoic acid hydrazide as a white solid. mp = 109 – 111 °C.

15 ^1H NMR ($\text{CHCl}_3\text{-d}1$) δ 7.41 – 7.51 (m, 2H), 6.97 (t, 1H, $J = 8.49$), 4.10 (t, 2H, $J = 6.72$ Hz), 2.43 (t, 2H, $J = 7.08$ Hz), 2.22 (s, 6H), 1.93 – 2.02 (m, 2H).

c) (3-{2-Fluoro-4-[5-(2-phenoxy-ethylsulfanyl-methyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine; maleic acid salt



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In a similar manner as exemplified in example 284 part c), 1.01 gm of 4-(3-dimethylamino-propoxy)-3-fluoro benzoic acid hydrazide was converted into 448 mg of (3-{2-fluoro-4-[5-(2-phenoxy-ethylsulfanyl)methyl]-[1,3,4]oxadiazol-2-yl}-phenoxy)-propyl)-dimethyl-amine; maleic acid salt as a beige solid. mp = 70 – 72 °C.

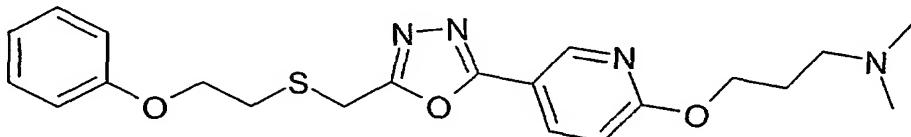
5 ¹H NMR (CH₃OH-d4) δ 7.76 (d, 1H, J = 8.85 Hz), 7.72 (d, 1H, J = 11.32 Hz), 7.26 (t, 1H, J = 8.49 Hz), 7.19 (t, 2H, J = 8.85 Hz), 6.84 – 6.90 (m, 3H), 6.22 (s, 2H), 4.26 (t, 2H, J = 5.66 Hz), 4.18 (t, 2H, J = 6.01 Hz), 4.13 (s, 2H), 3.35 (t, 2H, J = 7.43 Hz), 3.03 (t, 2H, J = 6.37 Hz), 2.93 (s, 6H), 2.23 – 2.32 (m, 2H).

Anal. Calcd for C₂₆H₃₀FN₃O₇S: C, 57.03; H, 5.52; N, 7.67. Found C, 56.68; H, 5.32; N,

10 7.71.

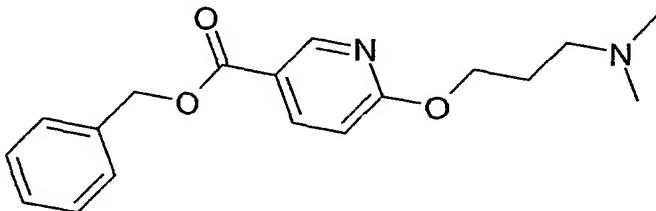
Example 288

Preparation of dimethyl-(3-{5-[5-(2-phenoxy-ethylsulfanyl)methyl]-[1,3,4]oxadiazol-2-yl}-pyridin-2-yloxy)-propyl)-amine



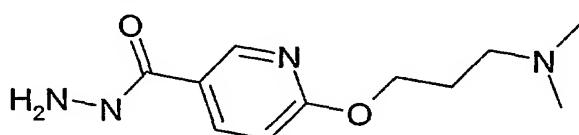
15

a) 6-(3-Dimethylamino-propoxy)-nicotinic acid benzyl ester



In a similar manner as exemplified for Example 283, part a), 5.0 gm of benzyl 6-hydroxynicotinate was converted into a 50:50 mixture of 6-(3-dimethylamino-propoxy)-nicotinic acid benzyl ester and it's N-alkylated isomer as a light yellow oil.

b) 6-(3-Dimethylamino-propoxy)-nicotinic acid hydrazide



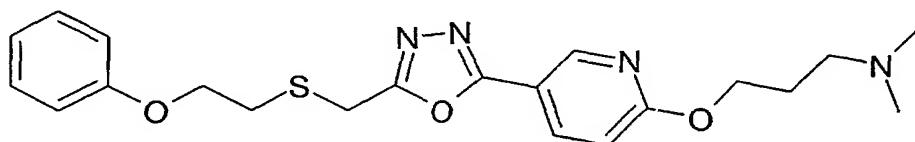
-518-

In a similar manner as exemplified in example 285 part b), 7.0 gm of a 50:50 mixture of 6-(3-dimethylamino-propoxy)-nicotinic acid benzyl ester and it's N-alkylated isomer were converted into a mixture of N- and O-alkylated hydrazides which was separated by chromatography on silica gel using a 0 to 10% gradient of a 2N ammonia in methanol mixture in methylene chloride. 1.96 gm of 6-(3-dimethylamino-propoxy)-nicotinic acid hydrazide was obtained as a white solid. mp = 81 – 83 °C.

¹H NMR (CHCl₃-d1) δ 8.50 (s, 1H), 7.93 (d, 1H, J = 10.61 Hz), 7.86 (bs, 1H), 6.73 (d, 1H, J = 8.85 Hz), 4.35 (t, 2H, J = 6.72 Hz), 2.45 (t, 2H, J = 7.08 Hz), 2.25 (s, 6H), 1.87 – 2.00 (m, 2H).

10

c) Dimethyl-(3-{5-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yloxy}-propyl)-amine



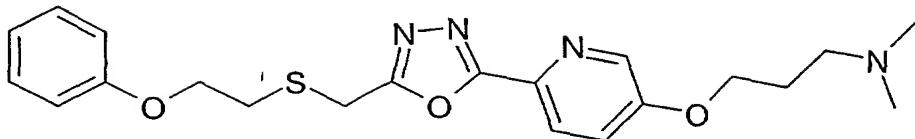
In a similar manner as exemplified in example 284, part c), 1.00 gm of 6-(3-dimethylamino-propoxy)-nicotinic acid hydrazide was converted into 774 mg of the free base dimethyl-(3-{5-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yloxy}-propyl)-amine as a white solid. mp = 69 - 70°C.

¹H NMR (CHCl₃-d1) δ 8.67 (d, 1H, J = 1.77 Hz), 8.13 (dd, 1H, J = 8.85, 2.48 Hz), 7.24 (t, 2H, J = 8.85), 6.92 (t, 1H, J = 7.43 Hz), 6.92 (t, 1H, J = 7.43 Hz), 6.86 (d, 2H, J = 7.78 Hz), 6.80 (d, 1H, J = 8.85 Hz), 4.40 (t, 2H, 6.72 Hz), 4.18 (t, 2H, J = 6.37 Hz), 4.03 (s, 2H), 3.03 (t, 2H, J = 6.01 Hz), 2.42 (t, 2H, J = 7.08 Hz), 2.24 (s, 6H), 1.91 – 1.99 (m, 2H). Anal. Calcd for C₂₁H₂₆N₄O₃S: C, 60.85; H, 6.32; N, 13.52. Found C, 61.07; H, 6.28; N, 13.46.

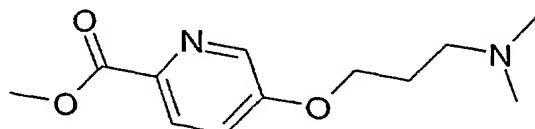
25

Example 289

Preparation of dimethyl-(3-{6-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-pyridin-3-yloxy}-propyl)-amine

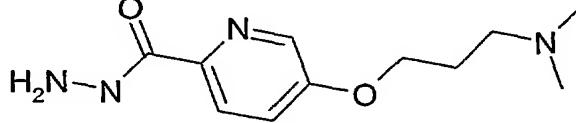


a) 5-(3-Dimethylamino-propoxy)-pyridine-2-carboxylic acid methyl ester



- 5 504.4 mg (3.29 mmol) of 5-hydroxy-pyridine-2-carboxylic acid methyl ester, 864 mg (3.29 mmol) of triphenylphosphine, and 390 uL of 3-dimethylaminopropan-1-ol were combined and stirred under dry nitrogen in 10 mL of dry THF at 0°C. 650 uL (3.29 mmol) of diisopropylazodicarboxylate was then slowly added over 3 minutes with continued stirring at 0°C for 1 hour and then at room temperature for a further 3 hours.
- 10 The solvents were removed under reduced pressure and the resultant oil was chromatographed on about 100 gm of silica gel using 240 ml of ethylacetate, then 500 ml of a gradient of from 0 to 5% of a 2N ammonia in methanol mixture in methylene chloride, and then 1L of a 5% 2N ammonia in methanol mixture in methylene chloride to give 602.3 mg (77%) of 5-(3-dimethylamino-propoxy)-pyridine-2-carboxylic acid methyl ester as a yellow waxy solid. mp = 44 – 45 °C.
- 15 ¹H NMR (CHCl₃-d1) δ 8.36 (d, 1H, J = 2.48 Hz), 8.07 (d, 1H, J = 8.85 Hz), 7.23 (dd, 1H, J = 8.84, 2.83 Hz), 4.11 (t, 2H, J = 6.37 Hz), 3.95 (s, 2H), 2.43 (t, 2H, J = 7.08 Hz), 2.23 (s, 6H), 1.93 – 2.01 (m, 2H).

- 20 b) 5-(3-Dimethylamino-propoxy)-pyridine-2-carboxylic acid hydrazide

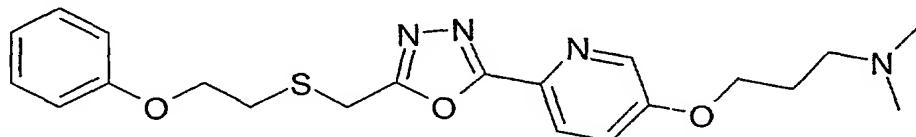


- In a similar manner as exemplified in example 285 part b), 1.4 gm of 5-(3-dimethylamino-propoxy)-pyridine-2-carboxylic acid methyl ester was converted into 1.38 gm of 5-(3-dimethylamino-propoxy)-pyridine-2-carboxylic acid hydrazide as a light brown waxy solid. mp = 82 – 83 °C.

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¹H NMR (CHCl₃-d1) δ 8.67 (bs, 1H), 8.16 (d, 1H, J = 2.48 Hz), 8.05 (d, 1H, J = 8.85 Hz), 7.25 (dd, 1H, J = 8.49, 2.83 Hz), 4.08 (t, 2H, J = 6.37 Hz), 2.42 (t, 2H, J = 7.08 Hz), 2.22 (s, 6H), 1.91 – 2.00 (m, 2H).

- 5 c) Dimethyl-(3-{6-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-pyridin-3-yloxy}-propyl)-amine



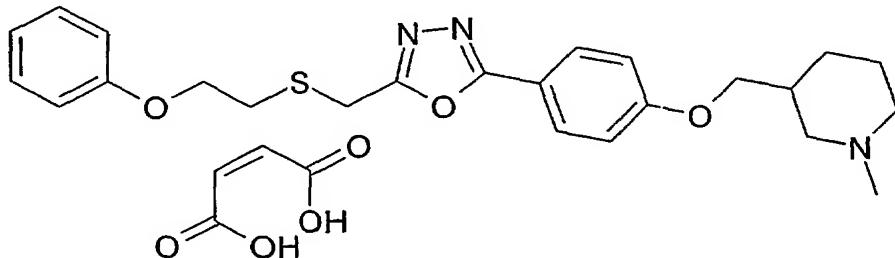
In a similar manner as exemplified for Example 283, part c), 1.00 gm of 5-(3-dimethylamino-propoxy)-pyridine-2-carboxylic acid hydrazide was converted into 712 mg
10 of the free base dimethyl-(3-{6-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-pyridin-3-yloxy}-propyl)-amine as a beige solid. mp = 47 – 49 °C.

¹H NMR (CHCl₃-d1) δ 8.40 (d, 1H, J = 2.83 Hz), 8.12 (d, 1H, J = 8.84 Hz), 7.80 (dd, 1H, J = 8.85, 2.83 Hz), 7.18 (t, 2H, J = 8.85 Hz), 6.92 (t, 1H, J = 7.43 Hz), 6.87 (d, 2H, J = 7.78 Hz), 4.18 (t, 2H, J = 6.01 Hz), 4.13 (t, 2H, J = 6.37 Hz), 4.04 (s, 2H), 3.04 (t, 2H, J = 6.37 Hz), 2.45 (t, 2H, J = 7.08 Hz), 2.24 (s, 6H), 1.94 – 2.03 (m, 2H).

15 Anal. Calcd for C₂₁H₂₆N₄O₃S: C, 60.85; H, 6.32; N, 13.52. Found C, 60.82; H, 6.24; N, 13.51.

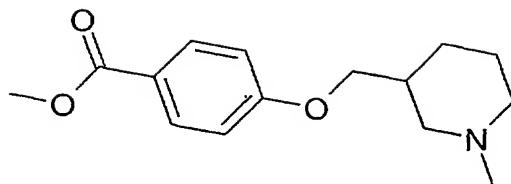
Example 290

20 Preparation of 1-methyl-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxyethyl}-piperidine; maleic acid salt



- a) 4-(1-Methyl-piperidin-3-ylmethoxy)-benzoic acid methyl ester

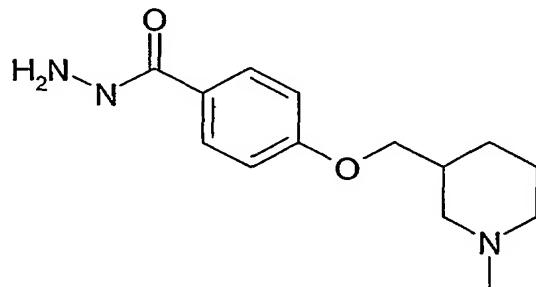
-521-



In a similar manner as exemplified for Example 283 part a), excepting that 3-hydroxymethyl-1-methyl-piperidine was substituted for the 3-dimethylaminopropan-1-ol and that the resultant material was purified by chromatography on about 100 gm of silica gel using 500 mL of ethylacetate, then 500 mL of a gradient of from 0 to 5% of a 2N ammonia in methanol mixture in methylene chloride, and then 1.8 L of a 5% 2N ammonia in methanol mixture in methylene chloride, 1.5 gm of methyl 4-hydroxybenzoate was converted into 1.792 gm of 4-(1-methyl-piperidin-3-ylmethoxy)-benzoic acid methyl ester as a white waxy solid. mp = 55 - 56°C.

10 ¹H NMR (CHCl₃-d1) δ 7.93 (d, 2H, J = 8.85 Hz), 6.86 (d, 2H, J = 8.85 Hz), 3.77 – 3.90 (m, 5H), 2.90 (d, 1H, J = 9.91 Hz), 2.71 (d, 1H, J = 10.97 Hz), 2.24 (s, 3H), 2.05 – 2.17 (m, 1H), 1.92 (bt, 1H), 1.53 – 1.84 (m, 4H), 1.07 (dq, 1H, J = 12.03, 3.54 Hz).

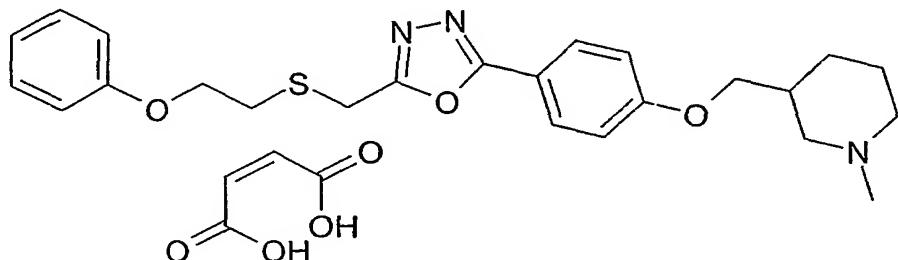
b) 4-(1-Methyl-piperidin-3-ylmethoxy)-benzoic acid hydrazide



15 In a similar manner as exemplified for Example 285, part b), 1.7 gm of 4-(1-methyl-piperidin-3-ylmethoxy)-benzoic acid methyl ester was converted into 1.7 gm of 4-(1-methyl-piperidin-3-ylmethoxy)-benzoic acid hydrazide as a white solid. mp = 170 - 172°C.

20 ¹H NMR (CHCl₃-d1) δ 7.67 (d, 2H, J = 8.84 Hz), 6.89 (d, 2H, J = 8.84 Hz), 4.04 (bs, 2H), 3.76 – 3.89 (m, 2H), 2.91 (bd, 1H, J = 10.61 Hz), 2.73 (bd, 1H, J = 10.97 Hz), 2.25 (s, 3H), 2.05 – 2.18 (m, 1H), 1.94 (bt, 1H, J = 10.97 Hz), 1.54 – 1.86 (m, 4H), 1.08 (dq, 1H, J = 11.32 Hz).

c) 1-Methyl-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxyethyl}-piperidine; maleic acid salt



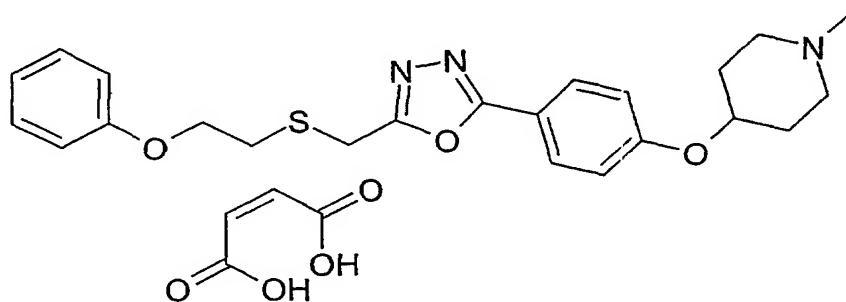
5

In a similar manner as exemplified for Example 285, part c), 800 mg of 4-(1-methyl-piperidin-3-ylmethoxy)-benzoic acid hydrazide was converted into 620 mg of 1-methyl-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxyethyl}-piperidine; maleic acid salt as a white solid. mp = 115 - 116°C.

- 10 ¹H NMR (CHCl₃-d1) δ 7.95 (d, 2H, J = 8.84 Hz), 7.25 (t, 2H, J = 8.85 Hz), 6.90 – 6.98 (m, 3H), 6.87 (d, 2H, J = 8.85 Hz), 6.27 (s, 2H), 4.19 (t, 2H, J = 6.37 Hz), 3.99 – 4.05 (m, 3H), 3.86 – 3.93 (m, 1H), 3.68 (bd, 1H, J = 12.38 Hz), 3.60 (bd, 1H, J = 11.32 Hz), 3.03 (t, 2H, J = 6.01 Hz), 2.82 (s, 3H), 2.50 – 2.73 (m, 3H), 1.91 – 2.15 (m, 3H), 1.48 (dq, 2H, J = 13.44, 4.60).
- 15 Anal. Calcd for C₂₈H₃₃N₃O₇S: C, 60.53; H, 5.99; N, 7.56. Found C, 60.76; H, 5.90; N, 7.62.

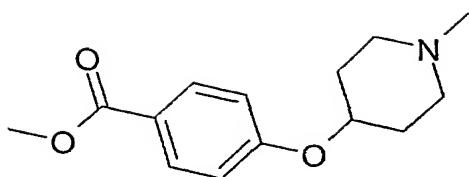
Example 291

Preparation of 1-methyl-4-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-piperidine; maleic acid salt



a) 4-(1-Methyl-piperidin-4-yloxy)-benzoic acid methyl ester

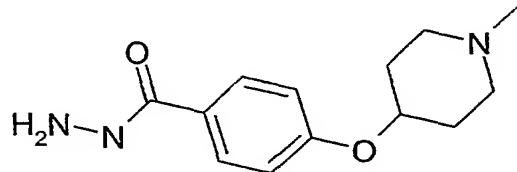
-523-



In a similar manner as exemplified in example 290, part a), except that 4-hydroxy-1-methyl-piperidine was substituted for 3-hydroxymethyl-1-methyl-piperidine, 1.5 gm of methyl 4-hydroxybenzoate was converted into 743mg of 4-(1-methyl-piperidin-4-yloxy)-
5 benzoic acid methyl ester.

¹H NMR (CHCl₃-d1) δ 7.93 (d, 2H, J = 9.20 Hz), 6.87 (d, 2H, J = 9.20 Hz), 4.33 – 4.42 (m, 1H), 3.84 (s, 3H), 2.59 – 2.71 (m, 2H), 2.21 – 2.32 (m, 5H), 1.93 – 3.02 (m, 2H), 1.76 – 1.88 (m, 2H).

10 b) 4-(1-Methyl-piperidin-4-yloxy)-benzoic acid hydrazide

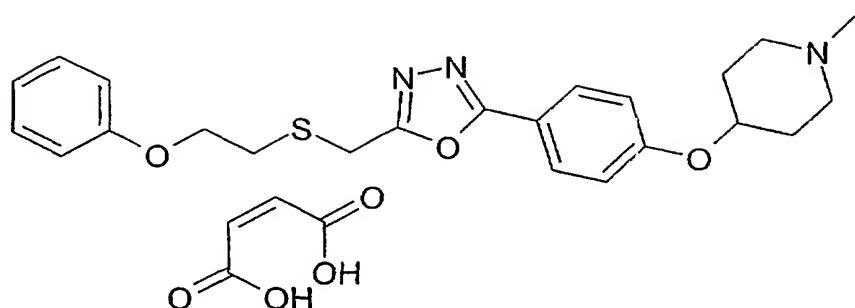


740 mg of 4-(1-methyl-piperidin-4-yloxy)-benzoic acid methyl ester was stirred in 3 ml of hydrazine hydrate and 3 ml of ethanol for 24 h. The solvents were removed under reduced pressure to yield 740 mg of 4-(1-methyl-piperidin-4-yloxy)-benzoic acid
15 hydrazide as a white solid. mp = 110 - 112°C.

¹H NMR (CHCl₃-d1) δ 7.66 (d, 2H, J = 8.85 Hz), 6.90 (d, 2H, J = 8.49 Hz), 4.31 – 4.41 (m, 1H), 4.04 (bs, 2H), 2.60 – 2.72 (m, 2H), 2.22 – 2.33 (m, 5H), 1.94 – 2.05 (m, 2H), 1.77 – 1.89 (m, 2H).

20 c) 1-Methyl-4-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-piperidine; maleic acid salt

-524-



In a similar manner as exemplified for example 284, part c), 684 mg of 4-(1-methyl-piperidin-4-yloxy)-benzoic acid hydrazide was converted into 897 mg of 1-methyl-4-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-piperidine; maleic acid salt as a yellow solid. mp = 149 - 150°C.

¹H NMR (CHCl₃-d1) δ 7.98 (d, 2H, J = 8.85 Hz), 7.25 (t, 2H, J = 7.43 Hz), 6.98 (d, 2H, J = 8.85 Hz), 6.93 (t, 1H, J = 7.08 Hz), 6.87 (d, 2H, J = 7.78 Hz), 6.28 (s, 2H), 4.78 (bs, 1H), 4.19 (t, 2H, J = 6.01 Hz), 4.03 (s, 2H), 3.37 – 3.49 (m, 2H), 3.07 – 3.21 (m, 2H), 3.03 (t, 2H, J = 6.01 Hz), 2.82 (s, 3H), 2.35 (bt, 2H, J = 13.44 Hz), 2.20 (bd, 2H, J = 15.21 Hz).

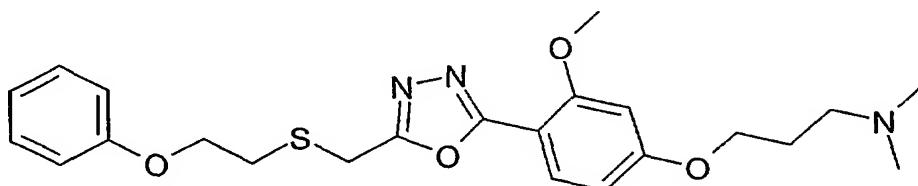
10

Anal. Calcd for C₂₇H₃₂N₃O₇S: C, 59.88; H, 5.77; N, 7.76. Found C, 59.85; H, 5.66; N, 7.63.

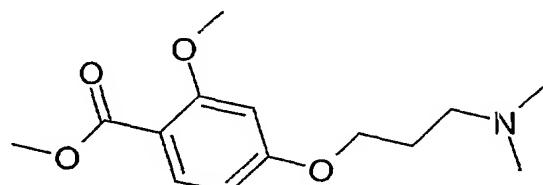
15

Example 292

Preparation of (3-{3-methoxy-4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine



a) Methyl 4-(3-dimethylamino-propoxy)-2-methoxy benzoate



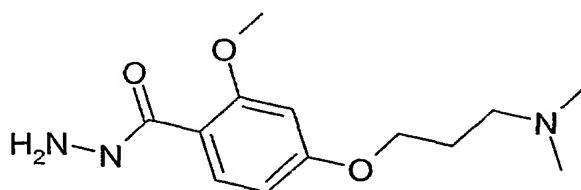
20

-525-

In a similar manner as exemplified for example 291, part a), 1.0 gm of methyl 2-methoxybenzoate was converted into 1.12 gm of methyl 4-(3-dimethylamino-propoxy)-2-methoxy benzoate as a clear oil.

¹H NMR (CHCl₃-d1) δ 7.80 (d, 1H, J = 9.20 Hz), 6.43 – 6.47 (m, 2H), 4.02 (t, 2H, J = 6.37 Hz), 3.85 (s, 3H), 3.81 (s, 3H), 2.41 (t, 2H, J = 7.07 Hz), 2.22 (s, 6H), 1.88 – 1.97 (m, 2H).

b) 4-(3-Dimethylamino-propoxy)-2-methoxy benzoic acid hydrazide

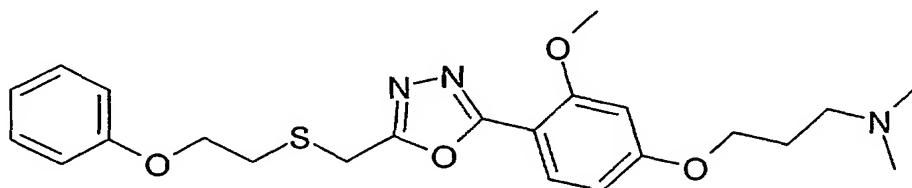


10 In a similar manner as exemplified in example 291, part b, 1.12 gm of methyl 4-(3-dimethylamino-propoxy)-2-methoxy benzoate was converted into 1.028 gm of 4-(3-dimethylamino-propoxy)-2-methoxy benzoic acid hydrazide as a white waxy solid. mp = 47 - 52°C.

¹H NMR (CHCl₃-d1) δ 7.98 (d, 1H, J = 8.49 Hz), 6.51 (dd, 1H, J = 8.85, 2.48 Hz), 6.42 (d, 1H, J = 2.48 Hz), 3.98 (t, 2H, J = 6.01 Hz), 3.87 (s, 3H), 2.48 (t, 2H, J = 7.43 Hz), 2.25 (s, 6H), 1.88 – 1.97 (m, 2H).

c) (3-{3-Methoxy-4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine

20



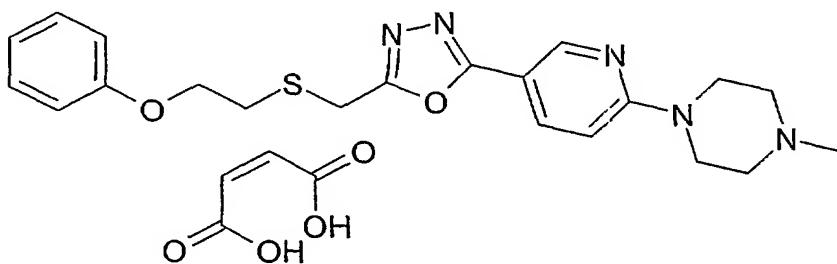
In a similar manner as exemplified for example 284, part c), 726 mg of 4-(3-dimethylamino-propoxy)-2-methoxy benzoic acid hydrazide was converted into 720 mg (3-{3-methoxy-4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine as the free base.

¹H NMR (CHCl₃-d1) δ 7.80 (d, 1H, J = 8.85 Hz), 7.24 (t, 2H, J = 7.43 Hz), 6.92 (t, 1H, J = 7.43 Hz), 6.86 (d, 2H, J = 8.85 Hz), 6.52 – 6.58 (m, 2H), 4.17 (t, 2H, J = 6.37 Hz), 4.06 (t, 2H, J = 6.37 Hz), 4.00 (s, 2H), 3.89 (s, 3H), 3.04 (t, 2H, J = 6.37 Hz), 2.44 (t, 2H, J = 7.08 Hz), 2.24 (s, 6H), 1.91 – 2.00 (m, 2H).

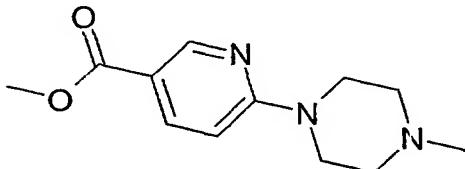
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Example 293

Preparation of 1-methyl-4-{5-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-piperazine; maleic acid salt



10 a) 6-(4-Methyl-piperazin-1-yl)-nicotinic acid methyl ester

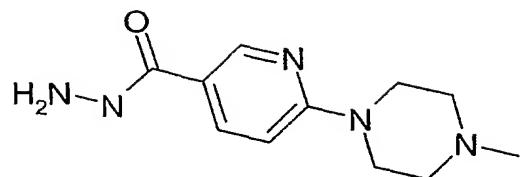


803.7 mg (4.69 mmol) of methyl 6-chloronicotinate, 570 uL (5.16 mmol) of N-methyl-piperidine, and 980 uL of diisopropylethylamine were and heated to 50°C in 10 mL of dry DMF for 24h. The mixture was then cooled and diluted with about 100 mL of ethylacetate which was then washed with about 30 mL of 2N NaOH, about 30 mL of brine. The organic fraction was dried over magnesium sulfate and then evaporated under reduced pressure to yield 1.1 gm of 6-(4-methyl-piperazin-1-yl)-nicotinic acid methyl ester as a yellow solid.

15 ¹H NMR (CHCl₃-d1) δ 8.76 (d, 1H, J = 2.12 Hz), 7.99 (dd, 1H, J = 8.85, 2.48 Hz), 6.56 (d, 1H, J = 9.20 Hz), 3.84 (s, 3H), 3.68 (t, 4H, J = 4.95 Hz), 2.48 (t, 4H, J = 4.95 Hz), 2.32 (s, 3H).

b) 6-(4-Methyl-piperazin-1-yl)-nicotinic acid hydrazide

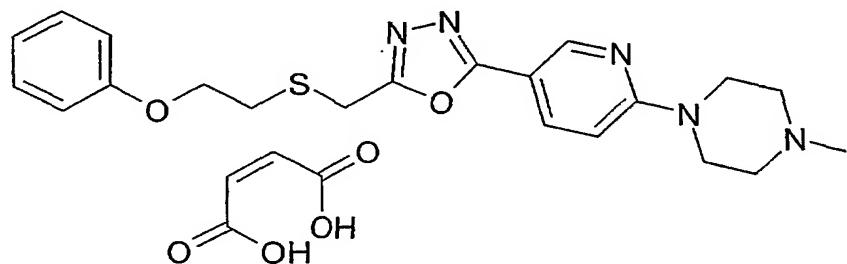
-527-



In a similar manner as exemplified for example 291, part b), 1.05 gm of 6-(4-methylpiperazin-1-yl)-nicotinic acid methyl ester was converted into 1.05 gm of 6-(4-methylpiperazin-1-yl)-nicotinic acid hydrazide as a waxy solid. mp = 170 - 171°C.

- 5 ¹H NMR (CHCl₃-d1) δ 8.50 (d, 1H, J = 2.12 Hz), 7.84 (dd, 1H, J = 8.85, 2.48 Hz), 7.13
 (bs, 1H), 6.60 (d, 1H, J = 8.85 Hz), 4.02 (bs, 1H), 3.65 (t, 4H, J = 5.81 Hz), 2.48 (t, 4H, J
 = 4.95 Hz), 2.32 (s, 3H).

- 10 c) 1-Methyl-4-{5-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-pyridin-2-
 yl}-piperazine; maleic acid salt



- 15 In a similar manner as exemplified for example 284, part c), 1.00 gm of 6-(4-methylpiperazin-1-yl)-nicotinic acid hydrazide was converted into 1.00 gm of 1-methyl-4-{5-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-piperazine; maleic acid salt as a white solid. mp = 146 - 147°C.

¹H NMR (CH₃OH-d4) δ 8.74 (d, 1H, J = 1.77 Hz), 8.09 (dd, 1H, J = 9.20, 2.12 Hz), 7.20
 (t, 2H, J = 8.14 Hz), 7.02 (d, 1H, J = 8.85 Hz), 6.83 – 6.90 (m, 3H), 6.23 (s, 2H), 4.17 (t,
 2H, J = 6.01 Hz), 4.13 (s, 2H), 3.33 (bs, 2H), 3.03 (t, 2H, J = 6.37 Hz), 2.91 (s, 3H).

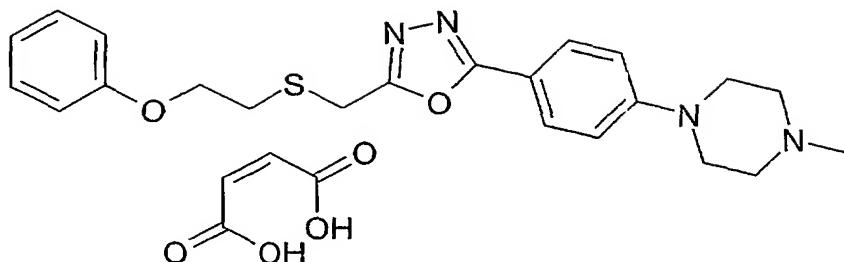
Anal. Calcd for C₂₅H₂₉N₅O₆S: C, 56.91; H, 5.54; N, 13.27. Found C, 56.85; H, 5.36; N,

20 13.19.

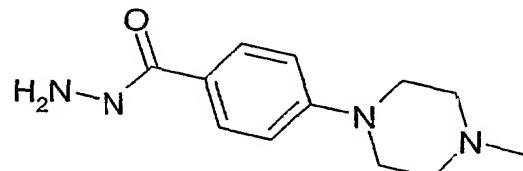
Example 294

Preparation of 1-methyl-4-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-piperazine; maleic acid salt

-528-



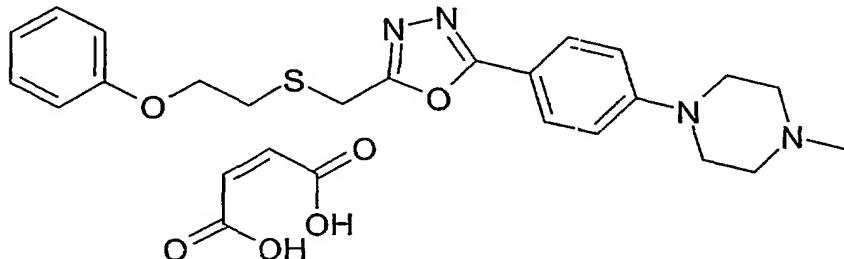
a) 4-(4-Methyl-piperazin-1-yl)-benzoic acid hydrazide



800 mg (3.41 mmol) of methyl 4-(4-methylpiperazino)benzenecarboxylate, 3 mL of
 5 hydrazine hydrate and 6 mL of ethanol were heated at 55°C for 24 hours at which time
 another 1 mL of hydrazine hydrate was added and heating was continued for another 24
 hours. The solvents were then removed under reduced pressure and the resultant solid
 was purified on about 100 gm of silica gel using a 0 to 10% gradient of a 2N ammonia in
 methanol mixture in methylene chloride, and then 1.8 L of a 10% 2N ammonia in
 10 methanol mixture in methylene chloride to give 620 mg of 4-(4-methyl-piperazin-1-yl)-
 benzoic acid hydrazide as a yellow waxy solid.

¹H NMR (CHCl₃-d1) δ 7.63 (d, 2H, J = 9.20 Hz), 7.27 (bs, 1H), 6.86 (d, 2H, J = 9.20 Hz),
 4.03 (bs, 2H), 3.28 (t, 4H, J = 4.95 Hz), 2.53 (t, 4H, J = 4.95 Hz), 2.32 (s, 3H).

15 b) 1-Methyl-4-{4-[5-(2-phenoxy-ethylsulfanyl)methyl]-[1,3,4]oxadiazol-2-yl}-phenyl-piperazine; maleic acid salt



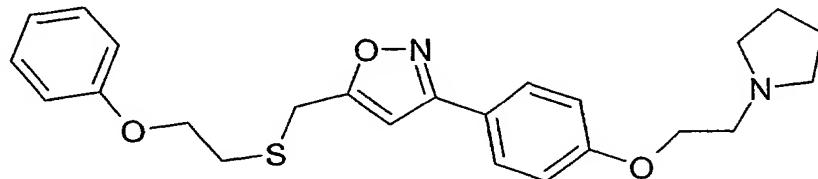
In a similar manner as exemplified in example 284, part c), 621 mg of 4-(4-methyl-piperazin-1-yl)-benzoic acid hydrazide was converted into 1.08 gm of 1-methyl-4-{4-[5-

(2-phenoxy-ethylsulfanyl methyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-piperazine; maleic acid salt as a yellow solid. mp = 151 – 152 °C.

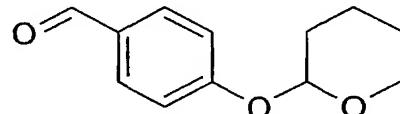
¹H NMR (CHCl₃-d1) δ 7.93 (d, 2H, J = 8.85 Hz), 7.25 (t, 2H, J = 8.49 Hz), 6.90 – 6.98
5 (m, 3H), 6.87 (d, 2H, J = 7.78 Hz), 6.27 (s, 2H), 4.18 (t, 2H, J = 6.19 Hz), 4.02 (s, 2H),
3.2 – 3.9 (bs, 6H), 3.03 (t, 2H, J = 6.19 Hz), 2.86 (s, 3H).

Example 295

Preparation of 5-(2-Phenoxy-ethylsulfanyl methyl)-3-[4-(2-pyrrolidin-1-yl-ethoxy)-
10 phenyl]-isoxazole

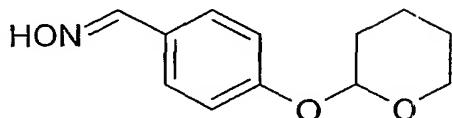


a) 4-(Tetrahydro-pyran-2-yloxy)-benzaldehyde



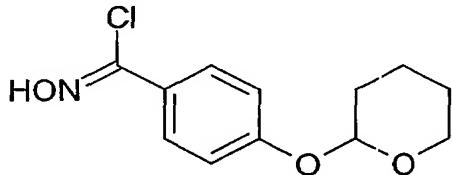
A round bottom flask was charged with 4-hydroxy-benzaldehyde (1.32 g, 10.8 mmol),
15 evacuated by vacuum pump and filled with N₂. The aldehyde was diluted with CH₂Cl₂ (15 mL) giving a cloudy mixture. 3,4-Dihydro-2H-pyran (1.5 mL, 16.2 mmol) was added by syringe, pyridinium p-toluenesulfonate (0.27 g, 1.1 mmol) was added neat and the reaction stirred at rt under N₂ for one hour. A reflux condenser was attached and the mixture stirred in a 45 °C oil bath overnight. The reaction was quenched with sat. aq.
20 NaHCO₃, the organic layer removed and the aqueous phase extracted with EtOAc (2X). The combined organics were dried over MgSO₄, filtered and concentrated. The crude product was purified by flash chromatography on silica gel (gradient EtOAc/Hexane 0%-80%) to give the title compound (0.87 g, 39%): ¹H NMR (CDCl₃): δ 9.88 (s, 1H), 7.82 (ap d, J = 8.8 Hz, 2H), 7.15 (ap d, J = 8.8 Hz, 2H), 5.54 (t, J = 3.1 Hz, 1H), 3.89-3.81 (m, 1H), 3.67-3.60 (m, 1H), 2.08-1.96 (m, 1H), 1.93-1.87 (m, 2H), 1.79-1.52 (m, 3H); TLC
25 (30% EtOAc/hexane) R_f 0.36.

b) 4-(Tetrahydro-pyran-2-yloxy)-benzaldehyde oxime



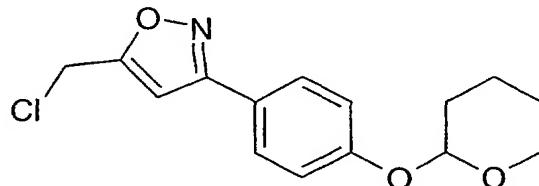
To a solution of 4-(tetrahydro-pyran-2-yloxy)-benzaldehyde (0.87 g, 4.2 mmol) in EtOH was added NaOAc·3H₂O (2.3 g, 16.9 mmol) and hydroxylamine hydrochloride (0.44 g, 6.3 mmol). The mixture was stirred at rt for 30 min, concentrated, diluted with sat. aq. NaHCO₃, and extracted with EtOAc (3 x). The combined organics were dried over MgSO₄, filtered and concentrated. The crude product was purified by flash chromatography on silica gel (gradient EtOAc/Hexane 0%-80%) to give predominantly one diastereomer as the title compound (0.63 g, 68%): ¹H NMR (CDCl₃): δ 8.08 (s, 1H), 7.50 (ap d, J = 8.9 Hz, 2H), 7.06 (ap d, J = 8.9 Hz, 2H), 5.46 (t, J = 3.2 Hz, 1H), 3.92-3.85 (m, 1H), 3.65-3.59 (m, 1H), 2.07-1.96 (m, 1H), 1.91-1.85 (m, 2H), 1.77-1.57 (m, 3H); TLC (30% EtOAc/hexane) R_f 0.29.

c) 4-(Tetrahydro-pyran-2-yloxy)-benzaldehyde chloro-oxime



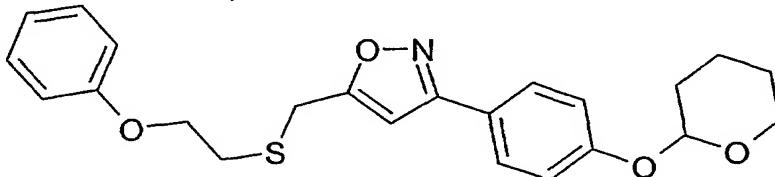
To a solution of 4-(Tetrahydro-pyran-2-yloxy)-benzaldehyde oxime (2.23 g, 10.1 mmol) in DMF at rt was added in one portion N-chlorosuccinimide (1.88 g, 14.1 mmol). After heating with a heat gun for 1 minute, the reaction went from a clear colorless solution to a clear light yellow solution. The reaction was stirred for 78 hours at rt, quenched with 50% sat. aq. NaCl, extracted with ether (3 x), dried over MgSO₄, filtered and concentrated. The crude product was azeotroped with xylenes (2 x) on the Rotovap to remove DMF and purified by flash chromatography on silica gel (gradient EtOAc/Hexane 0%-70%) to give the title compound contaminated with starting material (1.25 g): ¹H NMR (CDCl₃): δ 7.49-7.41 (m, 2H), 7.12-7.05 (m, 2H), 5.47 (ap q, 4H), 3.93-3.80 (m, 1H), 2.05-1.96 (m, 1H), 1.92-1.85 (m, 2H), 1.75-1.54 (m, 3H).

d) 5-Chloromethyl-3-[4-(tetrahydro-pyran-2-yloxy)-phenyl]-isoxazole



To a solution of 4-(tetrahydro-pyran-2-yloxy)-benzaldehyde chloro-oxime (1.25 g, 4.9 mmol) and 3-chloro-propyne (0.42 mL, 5.9 mmol) in ethyl acetate, DIPEA (1.02 mL, 5.9 mmol) was added slowly at rt, giving a cloudy suspension. The reaction was stirred for 16 hours then quenched with 80% sat. aq. NH₄Cl. After removal of the organic phase, the aqueous phase was extracted with EtOAc (2 x) and the combined organics dried over MgSO₄, filtered and concentrated. The crude product was purified by flash chromatography on silica gel (gradient EtOAc/Hexane 0%-70%) giving the title compound as the only regioisomer (1.10 g): ¹H NMR (CDCl₃): δ 7.72 (ap d, J = 8.9 Hz, 2H), 7.45 (m, 2H), 7.14-7.07 (m, 2H), 6.58 (s, 1H), 5.50-5.45 (m, 1H), 4.65 (s, 2H), 3.93-3.85 (m, 1H), 3.66-3.60 (m, 1H), 2.07-1.98 (m, 1H), 1.92-1.86 (m, 2H), 1.77-1.59 (m, 3H); TLC (30% EtOAc/Hexane) R_f 0.36.

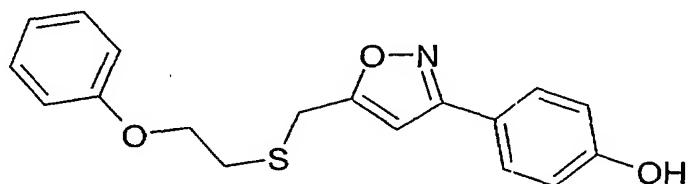
e) 5-(2-Phenoxy-ethylsulfanyl)methyl)-3-[4-(tetrahydro-pyran-2-yloxy)-phenyl]-isoxazole



An oven-dried round bottom flask was charged with NaH (60% in mineral oil, 0.13 g, 3.1 mmol), evacuated with a vacuum pump and filled with N₂. After dilution with anhydrous THF (10 mL), the flask was set in an ice-water bath and 2-phenoxy-ethanethiol (0.32 g, 2.09 mmol) in THF (5 mL) added slowly by syringe under N₂. The reaction was stirred 20 minutes at 0 °C, then removed from the bath and stirred 20 minutes at ambient temperature. 5-Chloromethyl-3-[4-(tetrahydro-pyran-2-yloxy)-phenyl]-isoxazole (0.68 g, 2.30 mmol) in THF (10 mL) was added by syringe, causing the reaction to change from colorless to yellow after 30 minutes. The reaction was stirred overnight then quenched with H₂O, diluted with hexane and the organic phase removed. The aqueous phase was extracted with EtOAc (2x), the combined organic phases were dried over MgSO₄, filtered

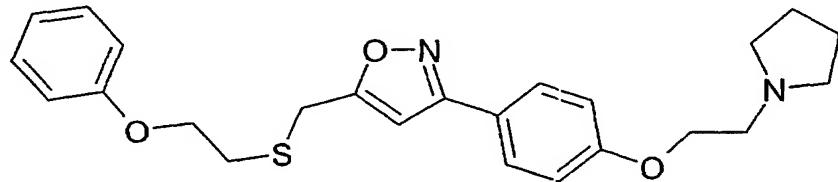
and concentrated. The crude product was purified by flash chromatography on silica gel (gradient EtOAc/Hexane 10%-50%) to give the title compound (0.51 g): ES-MS 412.1 (M+1), ¹H NMR (CDCl₃): δ 7.70 (ap d, J = 8.9 Hz, 2H), 7.31-7.25 (m, 2H), 7.11 (ap d, J = 8.9 Hz, 2H), 6.96 (ap t, 1H), 6.90 (ap d, J = 8.1 Hz, 2H), 6.44 (s, 1H), 5.49 (t, J = 3.3 Hz, 1H), 4.20 (t, J = 6.2 Hz, 2H), 3.96 (s, 2H), 3.94-3.86 (m, 1H), 3.66-3.60 (m, 1H), 2.99 (t, J = 6.2 Hz, 2H), 2.08-1.98 (m, 1H), 1.92-1.86 (m, 2H), 1.77-1.58 (m, 3H).

f) 4-[5-(2-Phenoxy-ethylsulfanylmethyl)-isoxazol-3-yl]-phenol



To a mixture of 5-(2-phenoxy-ethylsulfanylmethyl)-3-[4-(tetrahydro-pyran-2-yloxy)-phenyl]-isoxazole (0.51 g, 1.23 mmol) in ethanol was added pyridinium p-toluenesulfonate (0.03 g, 0.12 mmol). A reflux condenser was attached and the reaction stirred in a 50 °C oil bath for 3 hours. The mixture was concentrated and the crude product purified by flash chromatography on silica gel (10% EtOAc/Hexane) to give the title compound as a clear, colorless oil (0.39 g, 97%): ES-MS 328.1 (M+1), ¹H NMR (CDCl₃): δ 7.66 (ap d, J = 8.7 Hz, 2H), 7.30-7.25 (m, 2H), 6.99-6.88 (m, 5H), 6.44 (s, 1H), 5.33 (br s, 1H), 4.21 (t, J = 6.2 Hz, 2H), 3.96 (s, 2H), 3.00 (t, J = 6.2 Hz, 2H).

g) 5-(2-Phenoxy-ethylsulfanylmethyl)-3-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-isoxazole



An oven-dried round bottom flask was charged with 4-[5-(2-phenoxy-ethylsulfanylmethyl)-isoxazol-3-yl]-phenol (0.282 g, 0.86 mmol), evacuated with a vacuum pump and filled with N₂. Anhydrous DMF (5 mL) was added by syringe and after dissolution of the phenol the reaction was set in an ice-water bath and stirred 5 minutes. NaH (60% in mineral oil, 0.09 g, 2.24 mmol) was added neat. The mixture was

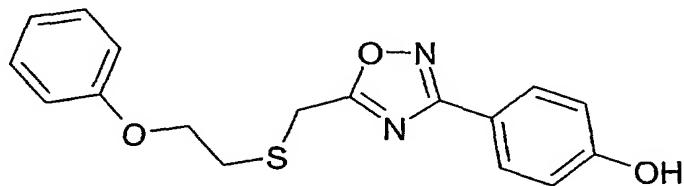
stirred 5 minutes at 0 °C, then removed from the bath and allowed to warm to rt. 1-(2-Chloro-ethyl)-pyrrolidine hydrochloride (0.176 g, 1.03 mmol) was added neat. A reflux condenser was attached and the mixture stirred 6 hours in a 50 °C oil bath. The reaction was quenched with 50% sat. aq. NaHCO₃ and the mixture extracted with EtOAc (3x).

- 5 The combined organics were washed with brine, dried over MgSO₄, filtered and concentrated, then azeotroped with xylenes on the Rotovap (2x) to remove DMF. The crude product was purified by flash chromatography on silica gel (gradient EtOAc/Hexane 30%-85%, 2N NH₃ in MeOH/EtOAc 5%) then crystallized in CH₂Cl₂/Ether/Hexane to give the title compound as fine white crystals (0.197 g, 54%).
- 10 ES-MS 425.1 (M+1), ¹H NMR (CDCl₃): δ 7.69 (ap d, J = 8.8 Hz, 2H), 7.30-7.25 (m, 2H), 7.00-6.94 (m, 3H), 6.91-6.88 (m, 2H), 6.44 (s, 1H), 4.22-4.17 (m, 4H), 3.96 (s, 2H), 3.02-2.93 (m, 4H), 2.70 (br s, 4H), 1.88-1.83 (m, 4H). Anal. calcd. for C₂₄H₂₈N₂O₃S: C, 67.90; H, 6.65; N, 6.60. Found: C, 67.97; H, 6.61; N, 6.67.

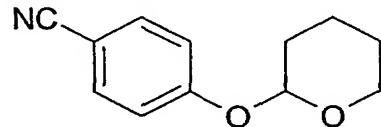
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Example 296

Preparation of 4-[5-(2-Phenoxy-ethylsulfanyl methyl)-[1,2,4]oxadiazol-3-yl]-phenol



a) 4-(Tetrahydro-pyran-2-yloxy)-benzonitrile

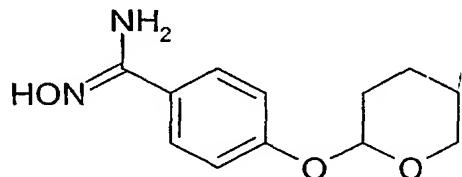


- 20 A solution of 4-cyanophenol (2.73 g, 22.9 mmol) in CH₂Cl₂ (15 mL) was treated with 3,4-dihydro-2H-pyran (4.19 mL, 45.8 mmol) and pyridinium p-toluenesulfonate (0.57 g, 2.29 mmol). A reflux condenser was attached and the mixture stirred in a 50 °C oil bath for 3 hours. After concentrating on the RotoVap, the crude product was purified by flash chromatography on silica gel (gradient EtOAc/ Hexane 0%-50%) to give a clear oil,
- 25 which crystallized neat to give the title compound as fine white crystals (4.35 g, 93%): ¹H NMR (CDCl₃): δ 7.57 (dt, J = 8.7, 2.4 Hz, 2H), 7.10 (dt, J = 8.7, 2.4 Hz, 2H), 5.49 (t, J =

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3.0 Hz, 1H), 3.85-3.77 (m, 1H), 3.65-3.59 (m, 1H), 2.04-1.92 (m, 1H), 1.90-1.84 (m, 2H), 1.77-1.50 (m, 3H); TLC (30% EtOAc/Hexane) *Rf* 0.47.

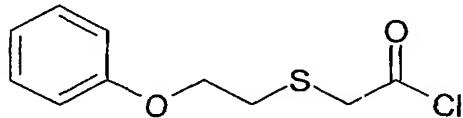
b) *N*-{Amino-[4-(tetrahydro-pyran-2-yloxy)-phenyl]-methyl}-hydroxylamine



5

A CEM reaction vial (for microwave reactions) with stir-bar was charged with 4-(tetrahydro-pyran-2-yloxy)-benzonitrile (3.14 g, 15.4 mmol). The nitrile was diluted with anhydrous ethanol (25 mL) and treated with hydroxylamine hydrochloride (1.61 g, 23.2 mmol) and ground NaOH (0.93 g, 23.2 mmol). A septum was attached and the reaction 10 microwaved in the CEM Discover reactor at 80 °C for 40 minutes (cooling on, average power 40 watts). The mixture was concentrated, diluted with H₂O, and extracted with EtOAc (3 x). The combined organics were washed with brine, dried over MgSO₄, filtered and concentrated. The crude product was purified by flash chromatography on silica gel (gradient EtOAc/Hexane 20%-100%) to give the title compound as a white foam (1.89 g, 15 52%): ES-MS 237.1 (M+1); ¹H NMR (CDCl₃): δ 7.55 (dt, J = 8.8, 2.5 Hz, 2H), 7.06 (dt, J = 8.8, 2.5 Hz, 2H), 5.46 (t, J = 3.0 Hz, 1H), 4.85 (br s, 2H), 3.92-3.85 (m, 1H), 3.65-3.58 (m, 1H), 2.05-1.96 (m, 1H), 1.91-1.85 (m, 2H), 1.76-1.57 (m, 3H).

c) (2-Phenoxy-ethylsulfanyl)-acetyl chloride

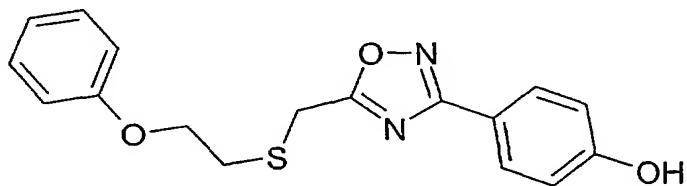


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An oven-dried round-bottom flask with stir-bar was charged with (2-phenoxy-ethylsulfanyl)-acetic acid (Maybridge, 5.57 g, 26.2 mmol). The flask was evacuated and filled with N₂. Anhydrous CH₂Cl₂ (20 mL) and DMF (4 drops) was added by syringe and the flask was set in an ice-water bath. Oxalyl chloride (2M/CH₂Cl₂, 26.2 mL, 52.4 mmol) 25 was added dropwise by syringe and the reaction stirred for 2 hours while the bath expired. The reaction mixture was concentrated then azeotroped with xylenes (remove DMF) on the RotoVap to give the title compound as a brown oil (6.57 g, 109%). ¹H NMR

(CDCl₃): δ 7.32-7.27 (m, 2H), 7.01-6.96 (m, 1H), 6.92-6.88 (m, 2H), 4.23 (t, J = 5.8 Hz, 2H), 3.91 (s, 2H), 3.05 (t, J = 5.8 Hz, 2H).

d) 4-[5-(2-Phenoxy-ethylsulfanyl)methyl]-[1,2,4]oxadiazol-3-yl]-phenol

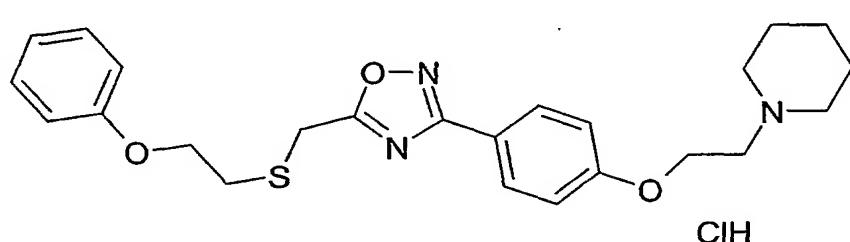


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In a CEM reaction vial with stir-bar a solution of N-{Amino-[4-(tetrahydro-pyran-2-yloxy)-phenyl]-methyl}-hydroxylamine (1.52 g, 6.43 mmol) in pyridine was treated with (2-phenoxy-ethylsulfanyl)-acetyl chloride (1.78 g, 7.72 mmol). The reaction was stirred at rt for 15 minutes, then microwaved in the CEM Discover reactor at 65 °C (cooling on) for 20 minutes and 80 °C (cooling on) for 30 minutes. The reaction mixture was transferred to a rb flask, concentrated then azeotroped with heptane on the RotoVap (2 x) to remove pyridine. The mixture was dissolved in ethanol, transferred to a CEM reaction vial and treated with pyridinium p-toluenesulfonate (0.16 g, 0.64 mmol). A septum was attached and the reaction microwaved at 55 °C (cooling on) for 10 minutes then 75 °C (cooling on) for 10 minutes. The mixture was concentrated on the RotoVap and purified by flash chromatography on silica gel (gradient EtOAc/Hexane 0-70%) to give the title compound as a clear yellow oil (1.37 g, 65%): ES-MS 329.1 (M+1), ¹H NMR (CDCl₃): δ 7.96 (dt, J = 8.9, 2.4 Hz, 2H), 7.30-7.25 (m, 2H), 6.98-6.88 (m, 5H), 5.49 (br s, 1H), 4.24 (t, J = 6.2 Hz, 2H), 4.05 (s, 2H), 3.11 (t, J = 6.2 Hz, 2H).

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Example 297
1-(2-{4-[5-(2-Phenoxy-ethylsulfanyl)methyl]-[1,2,4]oxadiazol-3-yl]-phenoxy)-ethyl-piperidine hydrochloride

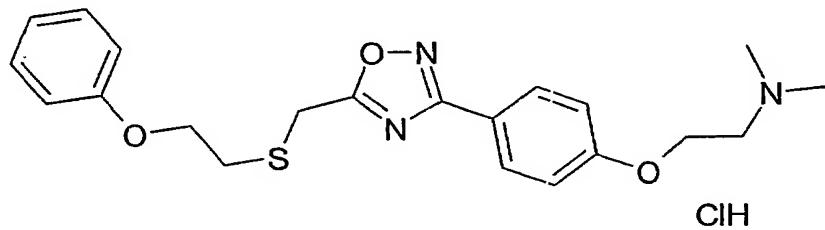


An oven-dried round bottom flask was charged with 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,2,4]oxadiazol-3-yl]-phenol (0.258 g, 0.78 mmol), evacuated with a vacuum pump and filled with N₂. Anhydrous DMF (5 mL) was added by syringe and after dissolution of the phenol the reaction was set in an ice-water bath. NaH (60% in mineral oil, 0.08 g, 2.0 mmol) was added neat. The mixture was stirred 1 minute at 0 °C, removed from the bath and stirred 5 minutes at rt. 1-(2-Chloro-ethyl)-piperidine hydrochloride (0.173 g, 0.94 mmol) was added neat, a reflux condenser was attached and the mixture stirred 1.5 hours in a 50 °C oil bath. The reaction was quenched with 50% sat. aq. NaHCO₃ and extracted with EtOAc (3x). The combined organics were washed with brine, dried over MgSO₄, filtered and concentrated, then azeotroped with xylenes on the Rotovap (2x) to remove DMF. The crude product was purified by flash chromatography on silica gel (gradient EtOAc/Hexane 30%-85%, 2N NH₃ in MeOH/EtOAc 5%) to give the free base as a clear oil. The free base was dissolved in ethanol and treated with 1M HCl/ether to give the title compound as white crystals. ES-MS 440.1 (M+1), ¹H NMR (DMSO d₆): δ 10.56 (s, 1H), 7.94 (dt, J = 8.8, 2.4 Hz, 2H), 7.25 (ap t, 2H), 7.16 (dt, J = 8.8 Hz, 2.4 Hz, 2H), 6.94-6.89 (m, 3H), 4.49 (t, J = 5.0 Hz, 2H), 4.26 (s, 2H), 4.20 (t, J = 6.3 Hz, 2H), 3.53-3.45 (m, 4H), 3.06 (t, J = 6.3 Hz, 2H), 3.03-2.94 (m, 2H), 1.84-1.76 (m, 4H), 1.69 (m, 1H), 1.44-1.33 (m, 1H). Anal. calcd. for C₂₄H₃₀ClN₃O₃S: C, 60.55; H, 6.35; N, 8.83. Found: C, 59.91; H, 5.90; N, 8.57.

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Example 298

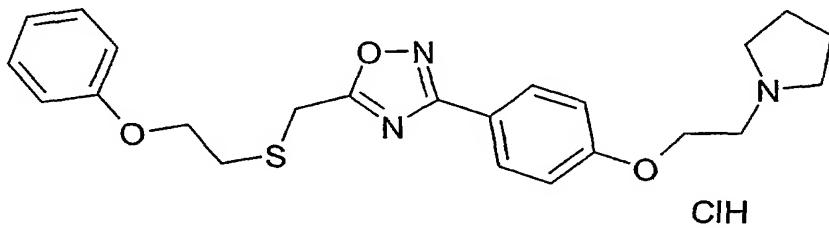
Dimethyl-(2-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,2,4]oxadiazol-3-yl]-phenoxy}-ethyl)-amine hydrochloride



25 A CEM reaction vessel was charged with NaH (60% in mineral oil, 0.15 g, 3.8 mmol). The vessel was capped with a septum and evacuated by a vacuum pump. DMF (3 mL) was added by syringe, the vessel filled with N₂ and set in an ice-water bath. 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,2,4]oxadiazol-3-yl]-phenol (0.422 g, 1.28 mmol) in

DMF (2 mL) was added dropwise by syringe. The mixture was stirred 5 minutes at 0 °C, removed from the bath and stirred 15 minutes at rt. The septum was removed, (2-chloroethyl)-dimethyl-amine hydrochloride (0.222 g, 1.54 mmol) was added neat, a new septum cap was attached and the reaction stirred 5 minutes at rt. The reaction was microwaved in the CEM Discover reactor at 70 °C (cooling on) for 20 minutes, then quenched with H₂O and extracted with EtOAc (3x). The combined organics were washed with brine, dried over MgSO₄, filtered and concentrated, then azeotroped with xylenes on the Rotovap (2x) to remove DMF. The crude product was purified by flash chromatography on silica gel (gradient EtOAc/Hexane 30%-85%, 2N NH₃ in MeOH/EtOAc 5%). The free base was dissolved in ethanol and treated with 1M HCl/ether to give the title compound as white crystals (0.230g, 41 %). ES-MS 400.1 (M+1), ¹H NMR (DMSO d₆): δ 10.26 (s, 1H), 7.95 (dt, J = 8.8, 2.5 Hz, 2H), 7.25 (ap t, 2H), 7.16 (dt, J = 8.8 Hz, 2.5 Hz, 2H), 6.94-6.89 (m, 3H), 4.43 (t, J = 5.0 Hz, 2H), 4.27 (s, 2H), 4.20 (t, J = 6.3 Hz, 2H), 3.52 (t, J = 5.0 Hz, 2H), 3.06 (t, J = 6.3 Hz, 2H), 2.85 (s, 6H). Anal. calcd. for C₂₁H₂₆ClN₃O₃S: C, 57.85; H, 6.01; N, 9.64. Found: C, 57.72; H, 5.90; N, 9.46.

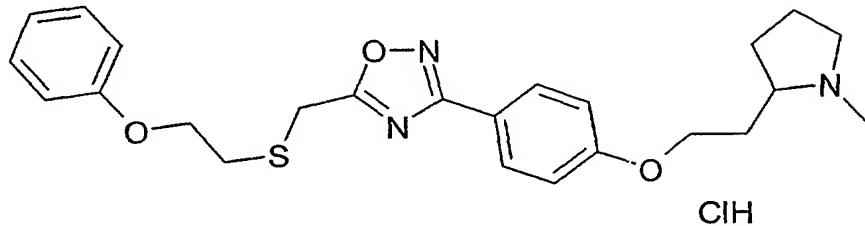
e) 5-(2-Phenoxy-ethylsulfanylmethyl)-3-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-[1,2,4]oxadiazole hydrochloride



The title compound was synthesized from 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,2,4]oxadiazol-3-yl]-phenol using a method similar to that described for dimethyl-(2-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,2,4]oxadiazol-3-yl]-phenoxy}-ethyl)-amine hydrochloride: ES-MS 426.1 (M+1), ¹H NMR (DMSO d₆): δ 10.39 (s, 1H), 7.95 (dt, J = 8.8, 2.5 Hz, 2H), 7.25 (ap t, 2H), 7.15 (dt, J = 8.8 Hz, 2.5 Hz, 2H), 6.94-6.89 (m, 3H), 4.40 (t, J = 5.0 Hz, 2H), 4.26 (s, 2H), 4.19 (t, J = 6.3 Hz, 2H), 3.63-3.54 (m, 4H), 3.16-3.03 (m, 4H), 2.05-1.96 (m, 2H), 1.94-1.83 (m, 2H). Anal. calcd. for C₂₃H₂₈ClN₃O₃S: C, 59.79; H, 6.11; N, 9.09. Found: C, 59.55; H, 6.15; N, 8.94.

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- e) 3-{4-[2-(1-Methyl-pyrrolidin-2-yl)-ethoxy]-phenyl}-5-(2-phenoxy-ethylsulfanylmethyl)-[1,2,4]oxadiazole hydrochloride



The title compound was synthesized from 4-[5-(2-phenoxy-ethylsulfanylmethyl)-

- 5 [1,2,4]oxadiazol-3-yl]-phenol using a method similar to that described for dimethyl-(2-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,2,4]oxadiazol-3-yl]-phenoxy}-ethyl)-amine hydrochloride: ES-MS 440.1 ($M+1$), ^1H NMR (DMSO d_6): δ 10.69 (m, 1H), 7.91 (ap t, 2H), 7.25 (ap t, 2H), 7.13-7.08 (m, 2H), 6.94-6.88 (m, 3H), 4.26 (s, 2H), 4.19 (t, $J = 6.2$ Hz, 2H), 3.48-3.29 (m, 1H), 3.18-2.99 (m, 4H), 2.82-2.73 (m, 3H), 2.46-1.69 (m, 7H).

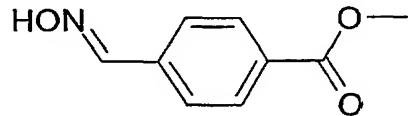
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Example 299

Preparation of 4-[5-(2-Phenoxy-ethylsulfanylmethyl)-isoxazol-3-yl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide

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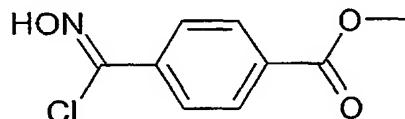
- a) 4-Hydroxyaminomethyl-benzoic acid methyl ester



To a solution of 4-formyl-benzoic acid methyl ester (4.18 g, 25.5 mmol) in EtOH was added NaOAc·3H₂O (6.93 g, 50.9 mmol) and hydroxylamine hydrochloride (2.65 g, 38.2 mmol). The mixture was stirred at rt for 1 hour, concentrated on the Rotovap, diluted with H₂O, and extracted with EtOAc (3 x). The combined organics were dried over MgSO₄, filtered and the solvent removed under vacuum to give a white residue as crude

(4.02 g, 88%): ^1H NMR (CDCl_3): δ 8.17 (s, 1H), 8.05 (ap d, $J = 8.5$ Hz, 2H), 7.65 (ap d, $J = 8.5$ Hz, 2H), 3.94 (s, 3H); TLC (20% EtOAc/Hexane) R_f 0.18

b) 4-(Chloro-hydroxyamino-methyl)-benzoic acid methyl ester

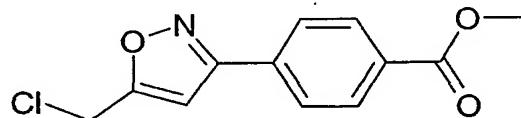


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To a solution of 4-hydroxyaminomethyl-benzoic acid methyl ester (4.02 g) in DMF at rt was added in five portions N-chlorosuccinimide (4.24 g, 31.7 mmol). After addition of the first portion, the reaction was heated with a heat gun for 10 seconds, giving a cloudy mixture. The remaining portions were added over 2 minutes. The reaction was stirred for 10 1 hour at rt, quenched with 70% sat. aq. NaCl, extracted with ether (3 x), dried over MgSO_4 , filtered and concentrated. The crude product was azeotroped with xylenes (2 x) to remove residual DMF, giving a white residue as crude product (5.56 g): ^1H NMR (CDCl_3): δ 9.04 (br s, 1H), 8.05 (ap d, $J = 8.8$ Hz, 2H), 7.92 (ap d, $J = 8.8$ Hz, 2H), 3.94 (s, 3H); TLC (20% EtOAc/Hexane) R_f 0.18

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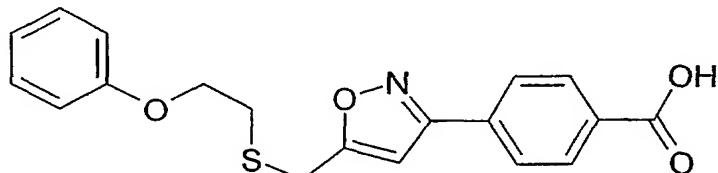
c) 4-(5-Chloromethyl-isoxazol-3-yl)-benzoic acid methyl ester



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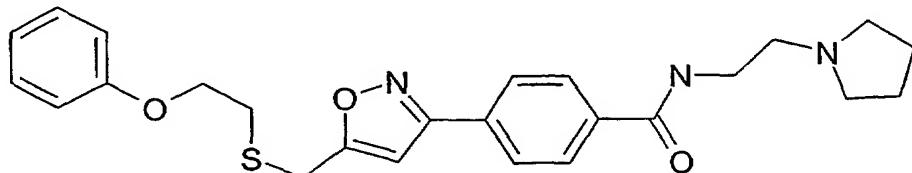
To a solution of 4-(chloro-hydroxyimino-methyl)-benzoic acid methyl ester (1.14 g, 5.35 mmol) and 3-chloro-propyne (0.46 mL, 6.42 mmol) in ethyl acetate TEA (0.89 mL, 6.42 mmol) was added slowly at rt, giving a cloudy mixture. The reaction was stirred for 16 hours then quenched with 75% sat. aq. NH_4Cl . After removal of the organic phase, the aqueous phase was extracted with EtOAc (2 x) and the combined organics dried over MgSO_4 , filtered and concentrated. The crude product was purified by flash chromatography on silica gel (gradient EtOAc/Hexane 0%-80%) giving the title compound as the only regioisomer (0.84 g, 62%). The structure of the regioisomer was confirmed by 1-D NOESY analysis: ES-MS 252.0 ($M+1$), ^1H NMR (CDCl_3): δ 8.13 (ap d, $J = 8.7$ Hz, 2H), 7.88 (ap d, $J = 8.7$ Hz, 2H), 6.69 (s, 1H), 4.68 (d, $J = 0.8$ Hz, 2H), 3.96 (s, 3H).

d) 4-[5-(2-Phenoxy-ethylsulfanyl methyl)-isoxazol-3-yl]-benzoic acid methyl ester



An oven-dried round bottom flask was charged with NaH (60% in mineral oil, 0.10 g, 2.5 mmol), evacuated with a vacuum pump and filled with N₂. After dilution with anhydrous THF (10 mL), the reaction was set in an ice-water bath and 2-phenoxy-ethanethiol (0.25 g, 1.6 mmol) in THF (20 mL) added slowly by syringe. The reaction was stirred 30 minutes at 0 °C, then removed from bath and allowed to warm to rt. 4-(5-Chloromethyl-isoxazol-3-yl)-benzoic acid methyl ester (0.45 g, 1.8 mmol) in THF (10 mL) was added by syringe, giving a cloudy yellow mixture. The reaction was stirred overnight then neutralized with 0.25 N HCl and extracted with EtOAc (3x). The combined organic phases were dried over MgSO₄, filtered and concentrated. The crude product was purified by flash chromatography on silica gel (gradient EtOAc/Hexane 30%-85%, MeOH/EtOAc 5%) to give the methyl ester of the title compound (0.16 g) and the title compound (0.20 g): ES-MS 356.0 (M+1), ¹H NMR (CDCl₃): δ 13.14 (br s, 1H), 8.07-7.93 (m, 5H), 7.29-7.21 (m, 2H), 7.01 (s, 1H), 6.94-6.88 (m, 2H), 4.16 (t, J = 6.4 Hz, 2H), 4.11 (s, 2H), 2.96 (t, J = 6.4 Hz, 2H).

e) 4-[5-(2-Phenoxy-ethylsulfanyl methyl)-isoxazol-3-yl]-N-(2-pyrrolidin-1-yl-ethyl)-benzamide

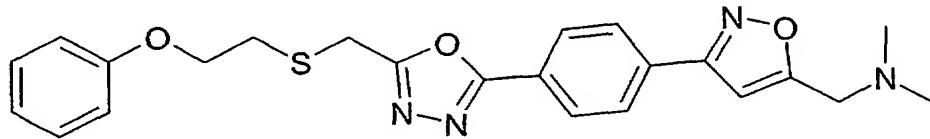


To a mixture of 4-[5-(2-phenoxy-ethylsulfanyl methyl)-isoxazol-3-yl]-benzoic acid (0.20 g, 0.55 mmol) in CH₂Cl₂ was added neat HOBr (0.11 g, 0.83 mmol), EDCI-HCl (0.16 g, 0.83 mmol), and DIPEA (0.19 mL, 1.11 mmol) at rt. 2-Pyrrolidin-1-yl-ethylamine (0.11 mL, 0.83 mmol) was added by syringe and the reaction stirred 1 hour. The reaction was

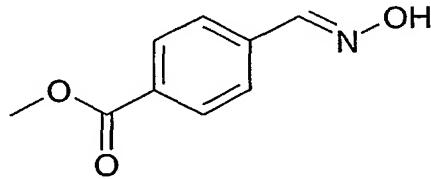
quenched with 50% sat. aq. NaHCO₃ and the organic phase removed. The aqueous phase was extracted with EtOAc (2x) and the combined organics dried over MgSO₄, filtered and concentrated. The crude product was purified by radial chromatography on silica gel (gradient EtOAc/Hexane 30%-85%, 2N NH₃ in MeOH/EtOAc 5%-20%) then repurified 5 by RP-HPLC to give the TFA salt. The salt was free-based with NaHCO₃ and crystallized in CH₂Cl₂/ether/hexane. The title compound was recovered as fine white crystals (0.029 g): ES-MS 452.3 (M+1), ¹H NMR (CDCl₃): δ 7.91-7.82 (m, 4H), 7.31-7.25 (m, 2H), 6.96 (ap t, J = 7.5 Hz, 1H), 6.90 (ap d, J = 8.0 Hz, 2H), 6.67 (s, 1H), 4.22 (t, J = 6.1 Hz, 2H), 3.99 (s, 2H), 3.64 (ap q, 2H), 3.01 (t, J = 6.1 Hz, 2H), 2.86 (br s, 2H), 2.74 (br s, 4H), 1.89 10 (br s, 4H). Anal. calcd. for C₂₅H₂₉N₃O₃S: C, 66.49; H, 6.47; N, 9.30. Found: C, 65.04; H, 6.20; N, 9.10.

Example 300

Preparation of Dimethyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-isoxazol-5-ylmethyl)-amine 15



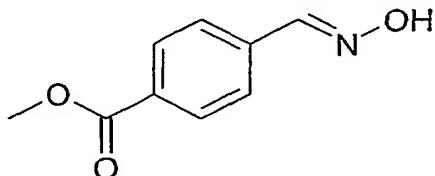
a) 4-(Hydroxyimino-methyl)-benzoic acid methyl ester



20 To a solution of 4-Formyl-benzoic acid methyl ester (Aldrich, 4.94 g, 30.1 mmol) in EtOH was added NaOAc·3H₂O (8.19 g, 60.2 mmol) and hydroxylamine hydrochloride (3.14 g, 45.1 mmol). The mixture was stirred at rt for 90 minutes, concentrated on the Rotovap, diluted with H₂O, and extracted with EtOAc (3 x). The combined organics were dried over MgSO₄, and the solvent removed under vacuum to give a white residue as crude (5.17 g): ¹H NMR (CDCl₃): δ 8.17 (s, 1H), 8.06 (ap d, J = 8.4 Hz, 2H), 7.85 (br s, 1H), 7.65 (ap d, J = 8.4 Hz, 2H), 3.93 (s, 3H).

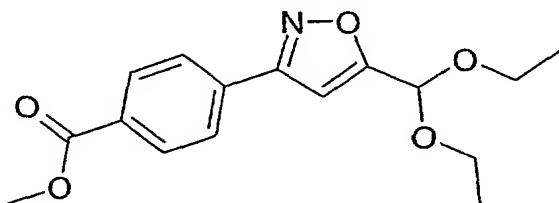
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b) 4-(Chloro-hydroxyimino-methyl)-benzoic acid methyl ester



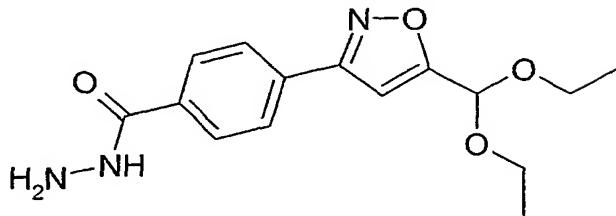
To a solution of 4-(Hydroxyimino-methyl)-benzoic acid methyl ester (5.17 g, 28.8 mmol) in DMF at rt was added in two portions N-chlorosuccinimide (4.24 g, 31.7 mmol). After addition of first portion, the reaction was heated with a heat gun for 10 seconds to give a cloudy mixture. The remaining portion was added and reaction became hotter (exotherm) for several minutes then slowly cooled. The reaction was stirred for 15 minutes at rt, quenched with 50% sat. aq. NaCl, extracted with ether (3 x), dried over MgSO₄, filtered and concentrated. The crude product was azeotroped with xylenes (2 x) to remove DMF, giving a white residue as the title compound (7.17 g): ES-MS 195.1 (M+1), ¹H NMR (CDCl₃): δ 9.10 (s, 1H), 8.06 (ap d, J = 8.5 Hz, 2H), 7.93 (ap d, J = 8.4 Hz, 2H), 3.93 (s, 3H).

c) 4-(5-Diethoxymethyl-isoxazol-3-yl)-benzoic acid methyl ester



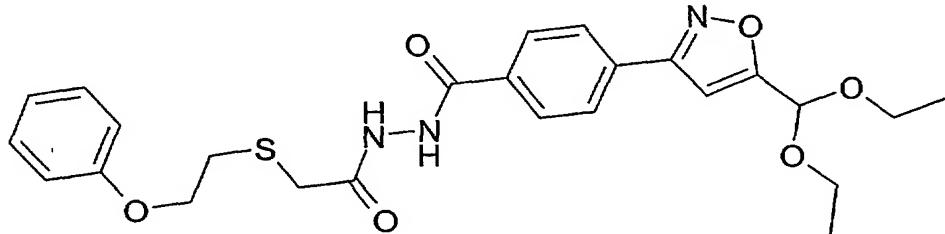
To a solution of 4-(Chloro-hydroxyimino-methyl)-benzoic acid methyl ester (7.17 g, 28.8 mmol) and 3,3-diethoxy-propyne (4.95 mL, 34.6 mmol) in ethyl acetate, TEA (4.82 mL, 34.6 mmol) was added slowly over 20 minutes at rt, giving a thick suspension. The reaction was stirred for 16 hours then quenched with H₂O. After removal of the organic phase, the aqueous phase was extracted with CH₂Cl₂ (2 x) and the combined organics dried over MgSO₄, filtered and concentrated. The crude product was purified by flash chromatography on silica gel (gradient EtOAc/Hexane 10% - 85%, 5% MeOH/EtOAc) giving the title compound (4.26 g): ES-MS 306.2 (M+1), ¹H NMR (CDCl₃): δ 8.12 (ap d, 2H), 7.89 (ap d, 2H), 6.71 (s, 1H), 5.69 (s, 1H), 3.69 (m, 4H), 1.28 (t, J = 7.0 Hz, 6H).

d) 4-(5-Diethoxymethyl-isoxazol-3-yl)-benzoic acid hydrazide



4-(5-Diethoxymethyl-isoxazol-3-yl)-benzoic acid methyl ester (4.26 g, 13.9 mmol) was diluted with isopropanol (25 mL) and hydrazine (2.0 mL, 70 mmol) was added by syringe under N₂. The mixture was refluxed in a 100 °C oil bath for 16 hours. The reaction was concentrated, then diluted with CH₂Cl₂ and concentrated (2 x) on Rotovap, then placed on high vacuum for 2 hours, giving the title compound as a thick oil (4.24 g): ¹H NMR (DMSO-d₆): δ 9.88 (br s, 1H), 7.95 (m, 4H), 7.14 (s, 1H), 5.80 (s, 1H), 3.63 (q, J = 7.1 Hz, 4H), 3.32 (br s, 2H), 1.19 (t, J = 7.1 Hz, 6H).

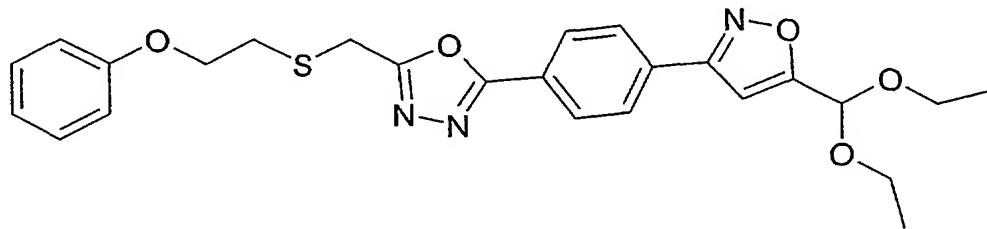
e) 4-(5-Diethoxymethyl-isoxazol-3-yl)-benzoic acid N'-[2-(2-phenoxy-ethylsulfanyl)-acetyl]-hydrazide



A mixture of (2-phenoxy-ethylsulfanyl)-acetic acid (Maybridge, 2.95 g, 13.9 mmol) and N,N'-carbonyldiimidazole (2.25 g, 13.9 mmol) in THF/MeCN 1:1 (15 mL) was heated at 60 °C for one hour, then allowed to cool to rt. 4-(5-Diethoxymethyl-isoxazol-3-yl)-benzoic acid hydrazide (4.24 g, 13.9 mmol) was added in one portion and the mixture stirred at rt under N₂ for 16 hours, then stirred at 50 °C for 4 hours. The reaction was poured into H₂O and extracted with EtOAc (1 x) and CH₂Cl₂ (2 x). The combined organics were dried over MgSO₄, filtered and concentrated. The crude product was purified by flash chromatography on silica gel (gradient EtOAc/Hexane 10%-85%, MeOH/EtOAc 5%-10%) to give the title compound (2.75 g): ES-MS 500.2 (M+1), ¹H NMR (CDCl₃): δ 9.54 (ap d, 1H), 9.06 (ap t, 1H), 7.84 (m, 4H), 7.30-7.23 (m, 2H), 6.98-

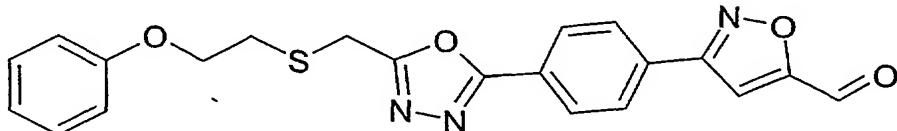
6.87 (m, 3H), 6.69 (s, 1H), 5.69 (s, 1H), 4.25 (t, $J = 5.8$ Hz, 2H), 3.69 (m, 4H), 3.51 (s, 2H), 3.10 (t, $J = 5.8$ Hz, 2H), 1.29 (t, $J = 7.0$ Hz, 6H).

f) 2-[4-(5-Diethoxymethyl-isoxazol-3-yl)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-
5 [1,3,4]oxadiazole



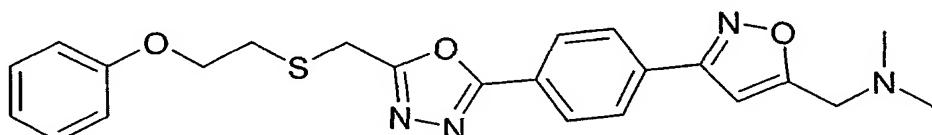
A mixture of 4-(5-diethoxymethyl-isoxazol-3-yl)-benzoic acid N'-[2-(2-phenoxy-ethylsulfanyl)-acetyl]-hydrazide (2.75 g, 5.5 mmol), triphenylphosphine (1.73 g, 6.6 mmol), and TEA (2.67 mL, 19.3 mmol) in THF was treated with carbon tetrabromide (2.19 g, 19.3 mmol) and stirred at rt under N_2 . After 1 hour, the reaction was heated to 50 °C and stirred 3 hours. The reaction was removed from heat and additional triphenylphosphine (0.29 g, 1.1 mmol) and carbon tetrabromide (0.36 g, 1.1 mmol) was added, then returned to heat and stirred for 16 hours. The mixture was concentrated, neutralized with sat. aq. NH_4Cl and extracted with EtOAc (3 x), dried over $MgSO_4$, filtered and concentrated. The resulting crude was purified by flash chromatography on silica gel (gradient CH_2Cl_2 /Hexane 50%-100%, MeOH/ CH_2Cl_2 2%-10%) then repurified (gradient EtOAc/Hexane 10%-50%) to give the title compound as an off-white residue (0.80 g): ES-MS 482.2 ($M+1$), 1H NMR ($CDCl_3$): δ 8.12 (ap d, $J = 8.5$ Hz, 2H), 7.96 (ap d, $J = 8.5$ Hz, 2H), 7.29-7.25 (m, 2H), 6.98-6.88 (m, 3H), 6.73 (s, 1H), 5.72 (s, 1H), 4.23 (t, $J = 6.1$ Hz, 2H), 4.09 (s, 2H), 3.70 (m, 4H), 3.08 (t, $J = 6.1$ Hz, 2H), 1.30 (t, $J = 7.0$ Hz, 6H).

g) 3-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-isoxazole-5-carbaldehyde



To a solution of 2-[4-(5-diethoxymethyl-isoxazol-3-yl)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole (0.80 g, 1.7 mmol) in acetic acid/H₂O (4:1, 25 mL) was added slowly 1 N aq. HCl (3 mL), giving a thick suspension. The mixture was stirred 5 minutes at rt, concentrated, diluted with acetone and concentrated (2 x), then placed on high vacuum to give the title compound: ES-MS 482.2 (M+33 consistent with aldehyde), ¹H NMR (CDCl₃): δ 10.06 (s, 1H), 8.16 (ap d, J = 8.4 Hz, 2H), 7.98 (ap d, J = 8.4 Hz, 2H), 7.35 (s, 1H), 7.30-7.24 (m, 2H), 6.98-6.87 (m, 3H), 4.23 (t, J = 6.2 Hz, 2H), 4.10 (s, 2H), 3.08 (t, J = 6.2 Hz, 2H).

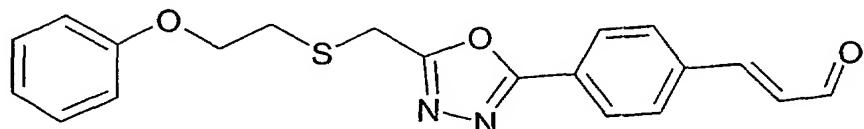
- 10 h) Dimethyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-isoxazol-5-ylmethyl)-amine



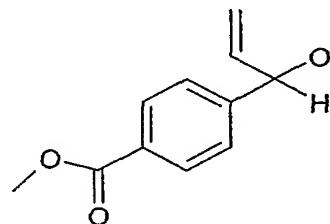
To a solution of 3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-isoxazole-5-carbaldehyde (0.14 g, 0.34 mmol) in 1,2-dichloroethane was added 15 dimethylamine (2 M/MeOH, 0.7 mL, 1.37 mmol) and finely ground NaBH(OAc)₃ (0.15 g, 0.69 mmol). The reaction was stirred 16 hours at rt, then heated to 60 °C and stirred 2 hours. Additional NaBH(OAc)₃ (0.08 g, 0.35 mmol) was added and the reaction stirred at 60 °C for 16 hours, then stirred at rt for 6 days. The reaction was quenched with H₂O and extracted with CH₂Cl₂ (2 x) and EtOAc (1 x), dried over MgSO₄, filtered and 20 concentrated. The crude product was purified by radial chromatography on silical gel (gradient EtOAc/Hexane 20%-85%), then crystallized in CH₂Cl₂/ether/hexane to give the title compound as fine, off-white crystals: ES-MS 437.2 (M+1), ¹H NMR (CDCl₃): δ 8.12 (ap d, J = 8.3 Hz, 2H), 7.94 (ap d, J = 8.4 Hz, 2H), 7.29-7.25 (m, 2H), 6.95 (ap t, J = 7.4 Hz, 1H), 6.90 (ap d, J = 8.3 Hz, 2H), 6.57 (s, 1H), 4.23 (t, J = 6.0 Hz, 2H), 4.09 (s, 2H), 3.71 (s, 2H), 3.08 (t, J = 6.0 Hz, 2H), 2.38 (s, 6H). Anal. calcd. for C₂₃H₂₄N₄O₃S: C, 63.28; H, 5.54; N, 12.83; O, 11.00; S, 7.35. Found: C, 62.95; H, 5.49; N, 12.70, O, 11.20; S, 7.60.

Example 301

Preparation of 3-{4-[5-(2-Phenoxy-ethylsulfanyl)methyl]-[1,3,4]oxadiazol-2-yl}-phenyl-propenal



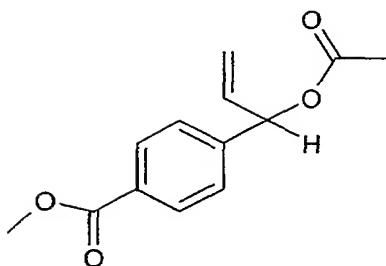
5 a) 4-(1-Hydroxy-allyl)-benzoic acid methyl ester



To a solution of 4-Formyl-benzoic acid methyl ester (Aldrich) (15.0 g, 91.40 mM) in 300 mL of THF at -78°C was added vinyl Grignard (Aldrich)(95.94 mL of a 1.0 molar solution in THF, 95.94 mM) dropwise via an addition funnel. The mixture was stirred at 10 -78°C for 3 h then warmed to RT and stirred for 18 h. The excess Grignard was quenched with 100 mL of sat NH₄Cl and diluted with 300 mL of methylene chloride and extracted three times with methylene chloride, one time with ethyl acetate and the combined organics were dried over MgSO₄. The material was filtered through paper and concentrated to a yellow liquid. The material was applied to a 65 mm Biotage flash 15 columb and eluted with a gradient of 1 L hexanes, 2 L 10% EtOAc in hexanes, 3 L 20% EtOAc in hexanes and 2 L 30% EtOAc in hexanes which upon concentrating provided 9.72 g of the 4-(1-Hydroxy-allyl)-benzoic acid methyl ester as a yellow liquid. ¹H NMR (CDCl₃, 300 MHz): δ 8.10 (d, 2H, J=8.1 Hz), 7.54 (d, 2H, J=8.1 Hz), 6.11 (ddd, 1H, J=18.0, 9.0, 6.6 Hz), 5.29-5.50 (m, 2H), 4.01 (s, 3H), 2.40 (s, 1H). TLC (50% 20 EtOAC/50%Hexanes) R_f 0.49.

b) 4-(1-Acetoxy-allyl)-benzoic acid methyl ester

-547-

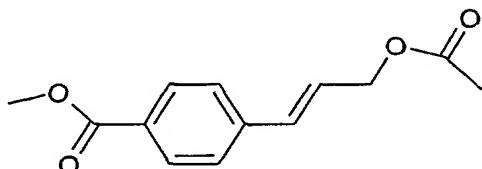


To a solution of 4-(1-Hydroxy-allyl)-benzoic acid methyl ester (2.3 g, 11.9 mM) in 36 mL of CH₂Cl₂ at rt was added pyridine (6 mL, 74 mmol), acetic anhydride (Aldrich)(3 mL, 32.0 mM) dropwise via a syringe and N,N-Dimethyl amino pyridine (20 mg, 0.16 mmol).

- 5 The mixture was stirred at rt for 18 h. The material was diluted with 100 mL of methylene chloride and extracted three times with methylene chloride, one time with ethyl acetate and the combined organics were dried over MgSO₄. The material was filtered through paper and concentrated to a yellow liquid. The material was applied to a 40 mm Biotage flash column and eluted with a gradient of 1 L hexanes, 1 L 10% EtOAc in
 10 hexanes, 2 L 20% EtOAc in hexanes and 1 L 30% EtOAc in hexanes which upon concentrating provided 2.7 g of the 4-(1-Acetoxy-allyl)-benzoic acid methyl ester as a yellow liquid. ¹H NMR (CDCl₃, 300 MHz): δ 8.03 (d, 2H, J=8.0 Hz), 7.42 (d, 2H, J=8.0 Hz), 6.32 (d, 1H, J=6.8 Hz), 6.0 (ddd, 1H, J = 15.6, 8.3, 5.9 Hz), 5.25-5.38 (m, 2H), 5.95 (s, 3H), 2.37 (s, 3H). TLC (50% EtOAC/50%Hexanes) R_f 0.60.

15

c) 4-(1-Acetoxy-allyl)-benzoic acid methyl ester

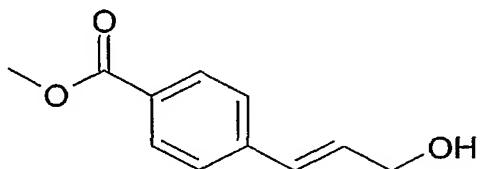


- A solution of 4-(1-Hydroxy-allyl)-benzoic acid methyl ester (11.83 g, 50.73 mM) in THF (150 mL) was treated with Bis(benzonitrile)dichloropalladium(II) (329 mg, 1.26 mM) at
 20 room temperature and stirred for 19 h. The material was poured through a plug of Celite 2cm and silica 2cm., concentrated and the crude yellow liquid solid was used directly (12g).

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¹H NMR (CDCl₃, 300 MHz): δ 8.02 (d, 2H, J = 7.2 Hz), 7.46 (d, 2H, J = 7.2 Hz), 6.70 (d, 1H, J=15 Hz), 6.41 (dt, 1H, J=15, 7.0 Hz), 4.78 (dd, 2H, J = 6.8, 0.5 Hz), 3.93 (s, 3H), 2.14 (s, 3H). TLC (50% EtOAc/50%Hexanes) R_f 0.60.

5 d) 4-(3-Hydroxy-propenyl)-benzoic acid methyl ester

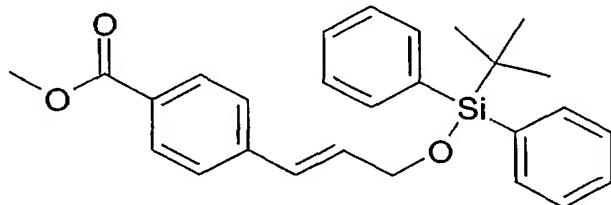


To a solution of 4-(3-acetoxy-propenyl)-benzoic acid methyl ester (6.85 g, 20.5 mmol) in MeOH was added p-toluenesulfonic acid monohydrate (0.55 g, 2.92 mmol). The mixture was stirred at 60 °C for 16 hours, concentrated on the Rotovap, neutralized with sat aq.

10 NaHCO₃, and extracted with EtOAc (3 x). The combined organics were washed with brine, dried over MgSO₄, and the solvent removed under vacuum to give a white residue as crude (5.34 g).

ES-MS 193.1 (M+1), ¹H NMR (CDCl₃): δ 7.98 (ap d, J = 8.4 Hz, 2H), 7.44 (ap d, J = 8.4 Hz, 2H), 6.67 (ap d, J = 15.9 Hz, 1H), 6.48 (dt, J = 15.9, 5.9 Hz, 1H), 4.37 (t, J = 5.1 Hz, 2H), 3.91 (s, 3H), 1.52 (ap t, 1H).

15 e) 4-[3-(tert-Butyl-diphenyl-silanyloxy)-propenyl]-benzoic acid methyl ester



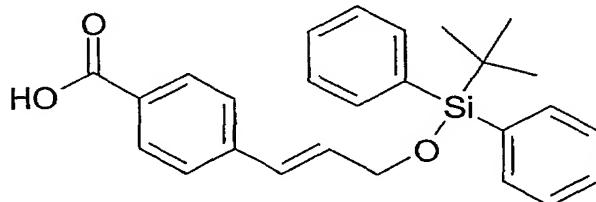
To a solution of 4-(3-hydroxy-propenyl)-benzoic acid methyl ester (5.85 g, 30.44 mmol)

20 in DMF (60 mL) was added imidazole (4.14 g, 60.9 mmol) and t-butyl-chlorodiphenylsilane (8.7 mL, 33.5 mmol). The mixture was stirred at rt for 1 hour and poured into 80% sat. aq. NH₄Cl (60 mL) and extracted with ether (3 x). The combined organics were dried over MgSO₄, filtered and concentrated under vacuum. The product was azeotroped with xylenes on the Rotovap to remove residual DMF, giving the title compound (14.76 g) as crude, which was used in the next step without further

-549-

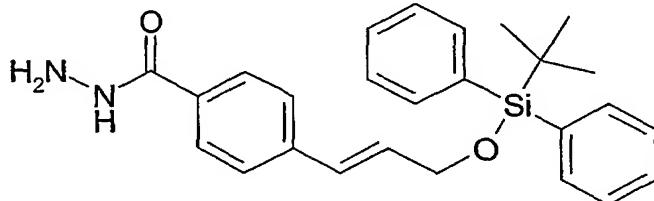
purification: ^1H NMR (CDCl_3): δ 7.98 (ap d, $J = 8.4$ Hz, 2H), 7.73-7.69 (m, 4H), 7.44-7.36 (m, 8H), 6.71 (ap d, $J = 16.0$ Hz, 1H), 6.39 (dt $J = 16.0, 4.5$ Hz, 1H), 4.40 (dd, $J = 4.5, 1.9$ Hz, 2H), 3.92 (s, 3H), 1.11 (s, 9H); TLC (30% EtOAc/Hexane) R_f 0.56.

5 f) 4-[3-(tert-Butyl-diphenyl-silyloxy)-propenyl]-benzoic acid



4-[3-(tert-Butyl-diphenyl-silyloxy)-propenyl]-benzoic acid methyl ester (17.49 g, 40.6 mmol) was diluted with ethanol (50 mL) and stirred for 10 minutes, then treated with 1.7 N NaOH (60 mL) and stirred at 45 °C for 4 hours, then 50 °C for 30 minutes. The 10 mixture was concentrated, neutralized with 5 N HCl to pH 7 and 1 N HCl to pH 3, and extracted with EtOAc (3 x). The combined organics were washed with brine, dried over MgSO₄, filtered and concentrated. The resulting crude was crystallized in MeOH/CH₂Cl₂/ether/hexane to remove desilylated byproduct. The supernatant was concentrated and purified by flash chromatography on silica gel (gradient EtOAc/hexane 10%-100%) 15 to give the title compound (9.52 g): ^1H NMR (CDCl_3): δ 8.06 (ap d, $J = 8.4$ Hz, 2H), 7.71 (m, 4H), 7.47-7.37 (m, 8H), 6.73 (ap d, $J = 15.9$ Hz, 1H), 6.42 (dt, $J = 15.9, 4.6$ Hz, 1H), 4.41 (dd, $J = 4.6, 1.8$ Hz, 2H), 1.11 (s, 9H).

g) 4-[3-(tert-Butyl-diphenyl-silyloxy)-propenyl]-benzoic acid hydrazide

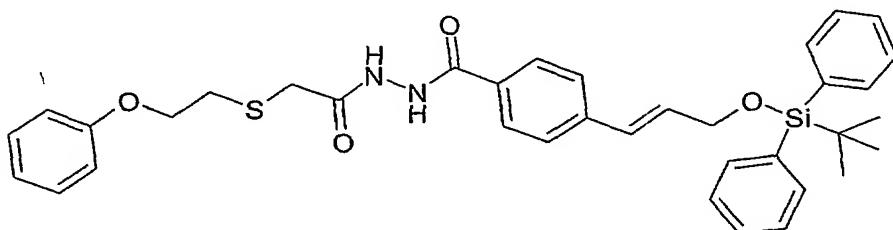


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A solution of 4-[3-(tert-butyl-diphenyl-silyloxy)-propenyl]-benzoic acid (9.52 g, 22.8 mmol) in THF/MeCN 1:1 (100 mL) was treated with N,N'-carbonyldiimidazole (3.89 g, 24.0 mmol) and heated at 60 °C for one hour. After cooling to rt, hydrazine (0.73 mL, 25.0 mmol) was added by syringe. The mixture was stirred for 1 hour at rt, concentrated,

diluted with 75% sat. aq. NH₄Cl, and extracted with EtOAc (3 x). The combined organics were washed with brine, dried over MgSO₄, filtered, and the solvent removed under vacuum to give the title compound (10.96 g) as crude, which was used in the next step without further purification: ¹H NMR (CDCl₃): δ 7.70 (m, 6H), 7.44-7.36 (m, 8H), 7.14 (s, 1H), 6.69 (ap d, J = 15.9 Hz, 1H), 6.37 (dt, J = 15.9, 4.6 Hz, 1H), 4.40 (dd, J = 4.6, 1.8 Hz, 2H), 1.11 (s, 9H).

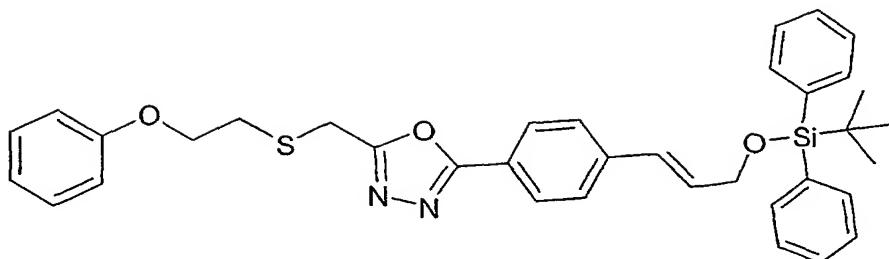
5 h) 4-[3-(tert-Butyl-diphenyl-silyloxy)-propenyl]-benzoic acid N'-[2-(2-phenoxy-ethylsulfanyl)-acetyl]-hydrazide



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A solution of (2-phenoxy-ethylsulfanyl)-acetic acid (Maybridge, 4.84 g, 22.8 mmol) in THF/MeCN 1:1 (60 mL) was treated with N,N'-carbonyldiimidazole (3.88g, 23.9 mmol) then heated at 60 °C for one hour. After cooling to rt, 4-[3-(tert-Butyl-diphenyl-silyloxy)-propenyl]-benzoic acid hydrazide (10.96 g, 22.8 mmol) was added neat. The mixture was stirred for 2 hours at rt, concentrated, diluted with 75% sat. aq. NH₄Cl, and extracted with EtOAc (3 x). The combined organics were washed with brine, dried over MgSO₄, filtered, and concentrated. The crude oil was purified by flash chromatography on silica gel (gradient EtOAc/Hexane 10%-50%) to give the title compound (12.09 g): ES-MS 625.4 (M+1); ¹H NMR (CDCl₃): δ 9.42 (d, J = 5.8 Hz, 1H), 8.59 (d, J = 5.8 Hz, 1H), 7.70 (m, 6H), 7.44-7.36 (m, 8H), 7.29-7.24 (m, 2H), 6.96-6.90 (m, 3H), 6.69 (ap d, J = 15.9 Hz, 1H), 6.38 (dt, J = 15.9, 4.6 Hz, 1H), 4.40 (dd, J = 4.7, 1.8 Hz, 2H), 4.26 (t, J = 5.9 Hz, 2H), 3.51 (s, 2H), 3.10 (t, J = 5.9 Hz, 2H), 1.11 (s, 9H).

20 i) 2-{4-[3-(tert-Butyl-diphenyl-silyloxy)-propenyl]-phenyl}-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole



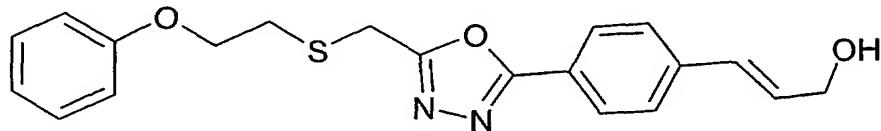
To a mixture of 4-[3-(tert-Butyl-diphenyl-silyloxy)-propenyl]-benzoic acid N'-(2-(2-phenoxy-ethylsulfanyl)-acetyl)-hydrazide (12.09 g, 19.3 mmol) and 2-chloro-1,3-dimethyl-2-imidazolinium hexafluorophosphate (5.66 g, 20.3 mmol) in anhydrous CH₂Cl₂

5 was slowly added DIPEA (7.4 mL, 42.6 mmol) by syringe. The mixture was stirred at rt for 72 hours, then quenched with 80% sat aq. NH₄Cl (120 mL). The organic phase was removed and the aqueous phase extracted with CH₂Cl₂ (1 x) and EtOAc (1 x). The combined organic phases were dried over MgSO₄, filtered and concentrated. The crude oil was purified by flash chromatography on silica gel (gradient EtOAc/Hexane 10%-10

10 50%) to give the title compound (9.09 g): ES-MS 607.4 (M+1); ¹H NMR (CDCl₃): δ 7.97 (ap d, J = 8.4 Hz, 2H), 7.71 (m, 4H), 7.48-7.37 (m, 8H), 7.30-7.25 (m, 2H), 6.95 (ap t, 1H), 6.90 (m, 2H), 6.71 (ap d, J = 15.9 Hz, 1H), 6.40 (dt, J = 15.9, 4.6 Hz, 1H), 4.41 (dd, J = 4.7, 1.8 Hz, 2H), 4.22 (t, J = 6.2 Hz, 2H), 4.07 (s, 2H), 3.07 (t, J = 6.2 Hz, 2H), 1.12 (s, 9H).

15

j) 3-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-prop-2-en-1-ol



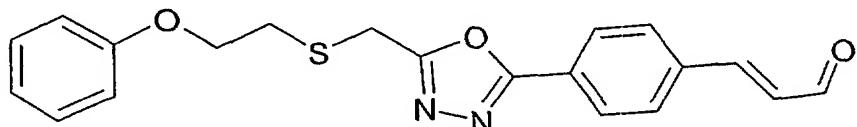
20 2-{4-[3-(tert-Butyl-diphenyl-silyloxy)-propenyl]-phenyl}-5-(2-phenoxy-ethoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole (9.09 g, 15.0 mmol) in anhydrous THF (100 mL)

was treated with tetrabutylammonium fluoride (1M/ THF, 18.7 mL, 18.7 mmol). The reaction was stirred at rt for 2.5 hours, then poured into water (80 mL). Hexane (25 mL) was added, the organic phase removed, and the aqueous phase extracted with EtOAc (2 x). The combined organics were washed with brine, dried over MgSO₄, filtered and concentrated. The resulting oil was purified by flash chromatography on silica gel

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(gradient EtOAc/Hexane 10%-60%) to give the title compound (4.25 g) as a white residue: ES-MS 369.1 (M+1); ¹H NMR (CDCl₃): δ 7.98 (ap d, J = 8.4 Hz, 2H), 7.50 (ap d, J = 8.4 Hz, 2H), 7.29-7.24 (m, 2H), 6.97-6.88 (m, 3H), 6.68 (ap d, J = 15.9 Hz, 1H), 6.50 (dt, J = 15.9, 4.6 Hz, 1H), 4.39 (dd, J = 5.3, 1.6 Hz, 2H), 4.22 (t, J = 6.1 Hz, 2H), 5 4.06 (s, 2H), 3.07 (t, J = 6.2 Hz, 2H).

k) 3-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-propenal

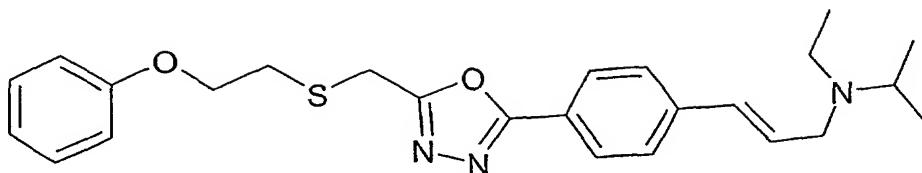


In an oven-dried round-bottom flask, a mixture of anhydrous CH₂Cl₂ (20 mL) and oxalyl chloride (2M/CH₂Cl₂, 3.93 mL, 7.86 mmol) was chilled to -78 °C in a dry ice/acetone bath and treated with DMSO (1.50 mL, 21.4 mmol) by slow addition with syringe. The mixture was stirred 20 minutes and 3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-prop-2-en-1-ol (2.63 g, 7.14 mmol) in CH₂Cl₂ (60 mL) was added slowly by syringe. The mixture was stirred 45 minutes at -78 °C and DIPEA (6.2 mL, 35.7 mmol) was added slowly by syringe. The mixture was stirred an additional 30 minutes, removed from bath and stirred 2 hours as it warmed to room temperature (rt). The reaction was neutralized with sat. aq. NH₄Cl (75 mL) and the organic layer removed. The aqueous phase was extracted with CH₂Cl₂ (1 x) and EtOAc (1 x), dried over MgSO₄, filtered and concentrated. The crude product was purified by chromatography on silica gel (gradient EtOAc/Hexane 10%-85%) to give the title compound (2.43 g): ES-MS 367.1 (M+1); ¹H NMR (CDCl₃): δ 9.76 (d, J = 7.7 Hz, 1H), 8.09 (ap d, J = 8.4 Hz, 2H), 7.69 (ap d, J = 8.4 Hz, 2H), 7.51 (d, J = 16.0 Hz, 1H), 7.29-7.24 (m, 2H), 6.98-6.88 (m, 3H), 6.80 (dd, J = 16.0, 7.5 Hz, 1H), 4.23 (t, J = 6.1 Hz, 2H), 4.09 (s, 2H), 3.08 (t, J = 6.1 Hz, 2H).

25

Example 302

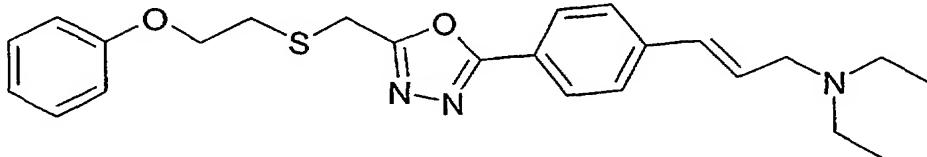
Ethyl-isopropyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-amine



To a solution of 3-{4-[5-(2-Phenoxy-ethylsulfanyl methyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-propenal (0.282 g, 0.77 mmol) in 1,2-dichloroethane was added ethyl-isopropyl-amine (0.11 mL, 0.92 mmol) and finely ground NaBH(OAc)₃ (0.20 g, 0.92 mmol). The reaction
5 was stirred 2 hours at rt, quenched with H₂O and the organic phase removed and passed through a Na₂SO₄ drying tube. The aqueous phase was extracted with EtOAc (2 x), the organic phases dried in the same manner and the combined organics concentrated. The crude product was purified by flash chromatography on silica gel (gradient
EtOAc/Hexane 50%-85%, 2N NH₃ in MeOH/EtOAc 15%), then crystallized in
10 CH₂Cl₂/ether/hexane to give the title compound as fine, white crystals (0.125 g) : ES-MS
438.2 (M+1), ¹H NMR (CDCl₃): δ 7.96 (ap d, J = 8.4 Hz, 2H), 7.48 (ap d, J = 8.4 Hz,
2H), 7.29-7.25 (m, 2H), 6.98-6.88 (m, 3H), 6.57 (d, J = 16.0 Hz, 1H), 6.45-6.37 (m, 1H),
4.22 (t, J = 6.2 Hz, 2H), 4.06 (s, 2H), 3.28 (d, J = 5.9 Hz, 2H), 3.06 (t, J = 6.2 Hz, 2H),
2.55 (ap q, 2H), 1.11-1.02 (m, 9H). Anal. calcd. for C₂₃H₂₄N₄O₃S: C, 68.62; H, 7.14; N,
15 9.60. Found: C, 68.44; H, 7.05; N, 9.55.

Example 303

Diethyl-(3-{4-[5-(2-phenoxy-ethylsulfanyl methyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-amine



20 The title compound was synthesized from 3-{4-[5-(2-phenoxy-ethylsulfanyl methyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-propenal using a method similar to that described for ethyl-isopropyl-(3-{4-[5-(2-phenoxy-ethylsulfanyl methyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-amine: ES-MS 424.2 (M+1), ¹H NMR (CDCl₃): δ 7.97 (ap d, J = 8.4 Hz,
2H), 7.48 (ap d, J = 8.4 Hz, 2H), 7.29-7.25 (m, 2H), 6.97-6.88 (m, 3H), 6.57 (d, J = 16.0
Hz, 1H), 6.48-6.39 (m, 1H), 4.22 (t, J = 6.0 Hz, 2H), 4.06 (s, 2H), 3.30 (d, J = 6.0 Hz,
2H), 3.07 (t, J = 6.0 Hz, 2H), 2.61 (q, J = 7.1 Hz, 4H), 1.09 (t, J = 7.1 Hz, 6H). Anal.
25

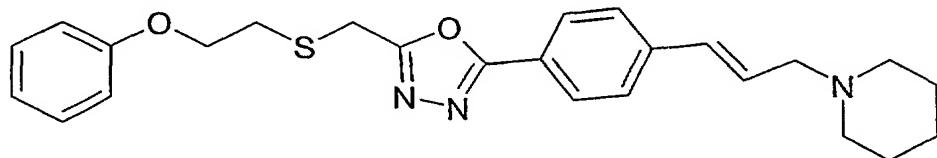
-554-

calcd. for C₂₄H₂₉N₃O₂S:

C, 68.05; H, 6.90; N, 9.92. Found: C, 67.94; H, 6.88; N, 9.73.

Example 304

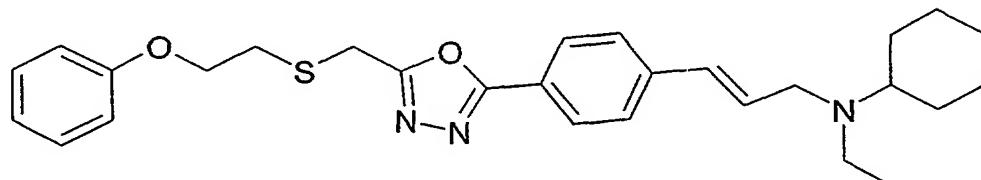
- 5 1-(3-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-piperidine



The title compound was synthesized from 3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-propenal using a method similar to that described for
10 Ethyl-isopropyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-amine: ES-MS 436.2 (M+1), ¹H NMR (CDCl₃): δ 7.96 (ap d, J = 8.4 Hz, 2H), 7.48 (ap d, J = 8.4 Hz, 2H), 7.29-7.24 (m, 2H), 6.95 (ap t, 1H), 6.90 (ap d, 2H), 6.57 (d, J = 16.0 Hz, 1H), 6.48-6.41 (m, 1H), 4.22 (t, J = 6.1 Hz, 2H), 4.06 (s, 2H), 3.17 (d, J = 6.1 Hz, 2H), 3.07 (t, J = 6.1 Hz, 2H), 2.47 (br s, 4H), 1.64 (m, 4H), 1.58 (br s, 2H). Anal.
15 calcd. for C₂₅H₂₉N₃O₂S: C, 68.93; H, 6.71; N, 9.65. Found: C, 68.33; H, 6.56; N, 9.42.

Example 305

Cyclohexyl-ethyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-amine



20 The title compound was synthesized from 3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-propenal using a method similar to that described for ethyl-isopropyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-amine: ES-MS 478.3 (M+1), ¹H NMR (CDCl₃): δ 7.96 (ap d, J = 8.4 Hz, 2H), 7.48 (ap d, J = 8.4 Hz, 2H), 7.29-7.24 (m, 2H), 6.95 (ap t, 1H), 6.90 (ap d, 2H), 6.55 (d, J = 16.1 Hz, 1H), 6.41 (m, 1H), 4.22 (t, J = 6.1 Hz, 2H), 4.06 (s, 2H), 3.33 (d, J = 5.8

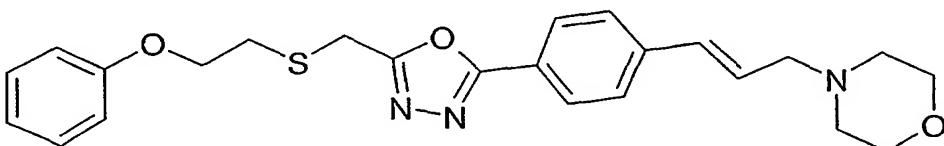
-555-

Hz, 2H), 3.07 (t, J = 6.1 Hz, 2H), 2.64-2.53 (m, 3H), 1.88-1.75 (m, 4H), 1.64 (ap d, J = 11.5 Hz, 2H), 1.25 (m, 4H), 1.06 (t, J = 7.1 Hz, 3H). Anal. calcd. for C₂₈H₃₅N₃O₂S: C, 70.41; H, 7.39; N, 8.80; Found: C, 69.92; H, 7.32; N, 8.65.

5

Example 306

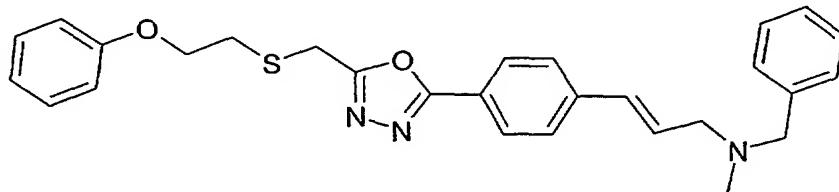
4-(3-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-morpholine



The title compound was synthesized from 3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-propenal using a method similar to that described for ethyl-isopropyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-amine: ES-MS 438.3 (M+1), ¹H NMR (CDCl₃): δ 7.97 (ap d, J = 8.2 Hz, 2H), 7.48 (ap d, J = 8.2 Hz, 2H), 7.29-7.24 (m, 2H), 6.95 (ap t, 1H), 6.89 (ap d, 2H), 6.59 (d, J = 16.0 Hz, 1H), 6.40 (m, 1H), 4.22 (t, J = 6.1 Hz, 2H), 4.06 (s, 2H), 3.76 (ap t, J = 4.5 Hz, 4H), 3.20 (d, J = 6.6 Hz, 2H), 3.07 (t, J = 6.2 Hz, 2H), 2.53 (br s, 4H). Anal. calcd. for C₂₄H₂₇N₃O₃S: C, 65.88; H, 6.22; N, 9.60. Found: C, 65.61; H, 6.18; N, 9.56.

Example 307

Benzyl-methyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-amine



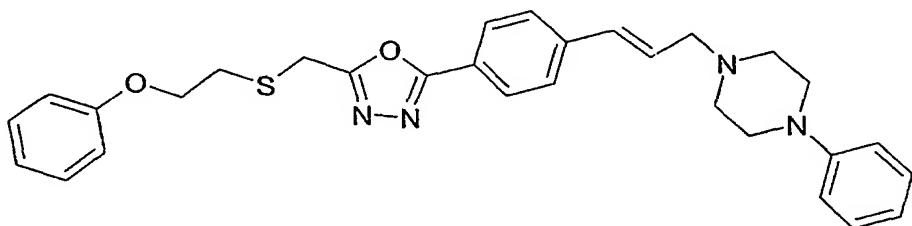
The title compound was synthesized from 3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-propenal using a method similar to that described for ethyl-isopropyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-amine: ES-MS 472.3 (M+1), ¹H NMR (CDCl₃): δ 7.97 (ap d, J = 8.6 Hz, 2H), 7.48 (ap d, J = 8.5 Hz, 2H), 7.36-7.31 (m, 4H), 7.29-7.24 (m, 3H), 6.98-6.87 (m,

3H), 6.59 (d, J = 16.1 Hz, 1H), 6.48-6.40 (m, 1H), 4.22 (t, J = 6.2 Hz, 2H), 4.06 (s, 2H), 3.58 (br s, 2H), 3.23 (d, J = 6.2 Hz, 2H), 3.06 (t, J = 6.2 Hz, 2H), 2.28 (s, 3H). Anal. calcd. for C₂₈H₂₉N₃O₂S: C, 71.31; H, 6.20; N, 8.91. Found: C, 70.81; H, 6.20; N, 8.75.

5

Example 308

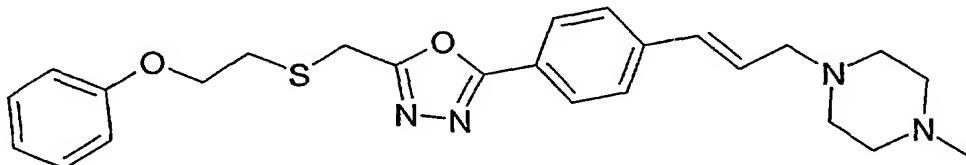
1-(3-{4-[5-(2-Phenoxy-ethylsulfanyl methyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-4-phenyl-piperazine



The title compound was synthesized from 3-{4-[5-(2-phenoxy-ethylsulfanyl methyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-propenal using a method similar to that described for ethyl-isopropyl-(3-{4-[5-(2-phenoxy-ethylsulfanyl methyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-amine: ES-MS 513.3 (M+1), ¹H NMR (CDCl₃): δ 7.98 (ap d, J = 8.4 Hz, 2H), 7.50 (ap d, J = 8.4 Hz, 2H), 7.29-7.24 (m, 4H), 6.98-6.84 (m, 6H), 6.62 (d, J = 16.0 Hz, 1H), 6.45 (m, 1H), 4.22 (t, J = 6.2 Hz, 2H), 4.06 (s, 2H), 3.26 (m, 6H), 3.07 (t, J = 6.2 Hz, 2H), 2.70 (ap t, 4H). Anal. calcd. for C₃₀H₃₂N₄O₂S: C, 70.28; H, 6.29; N, 10.93. Found: C, 70.26; H, 6.28; N, 10.92.

Example 309

1-Methyl-4-(3-{4-[5-(2-phenoxy-ethylsulfanyl methyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-piperazine



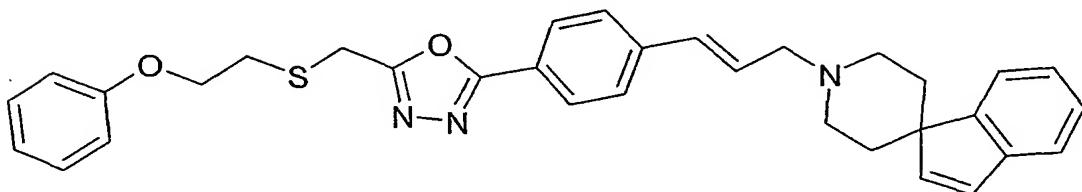
The title compound was synthesized from 3-{4-[5-(2-phenoxy-ethylsulfanyl methyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-propenal using a method similar to that described for ethyl-isopropyl-(3-{4-[5-(2-phenoxy-ethylsulfanyl methyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-amine: ES-MS 451.3 (M+1), ¹H NMR (CDCl₃): δ 7.97 (ap d, J = 8.4 Hz,

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2H), 7.47 (ap d, J = 8.4 Hz, 2H), 7.29-7.24 (m, 2H), 6.95 (ap t, 1H), 6.90 (ap d, 2H), 6.58 (d, J = 15.8 Hz, 1H), 6.41 (m, 1H), 4.22 (t, J = 6.3 Hz, 2H), 4.06 (s, 2H), 3.22 (d, J = 6.8 Hz, 2H), 3.07 (t, J = 6.2 Hz, 2H), 2.54 (br s, 8H), 2.33 (s, 3H). Anal. calcd. for C₂₅H₃₀N₄O₂S: C, 66.64; H, 6.71; N, 12.43. Found: C, 66.08; H, 6.71; N, 12.17.

5

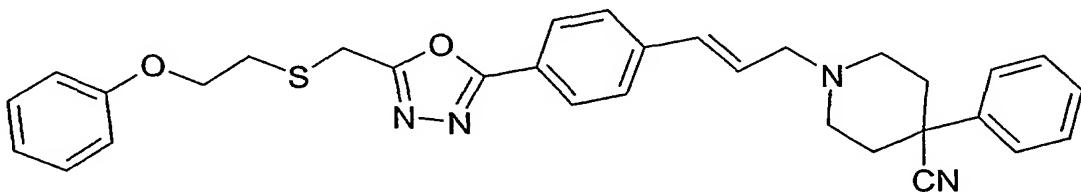
Example 310



The title compound was synthesized from 3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-propenal using a method similar to that described for
10 ethyl-isopropyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-amine: ES-MS 536.4 (M+1), ¹H NMR (CDCl₃): δ 7.98 (ap d, J = 8.5 Hz, 2H), 7.51 (ap d, J = 8.5 Hz, 2H), 7.39 (d, J = 7.0 Hz, 1H), 7.34-7.18 (m, 5H), 6.98-6.85 (m, 3H), 6.76 (d, J = 5.7 Hz, 1H), 6.63 (d, J = 15.8 Hz, 1H), 6.56-6.41 (m, 1H), 4.22 (t, J = 6.2 Hz, 2H), 4.06 (s, 2H), 3.35 (ap d, 2H), 3.12-3.05 (m, 4H), 2.43 (ap t, 2H), 2.25 (ap t, 2H), 1.42 (ap d, 2H). Anal. calcd. for C₃₃H₃₃N₃O₂S: C, 73.99; H, 6.21; N, 7.84. Found: C, 72.89; H, 6.04; N, 7.69.

Example 311

20 1-(3-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-4-phenyl-piperidine-4-carbonitrile



The title compound was synthesized from 3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-propenal using a method similar to that described for
25 ethyl-isopropyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-amine: ES-MS 537.2 (M+1), ¹H NMR (CDCl₃): δ 7.99 (ap d, J = 8.4 Hz,

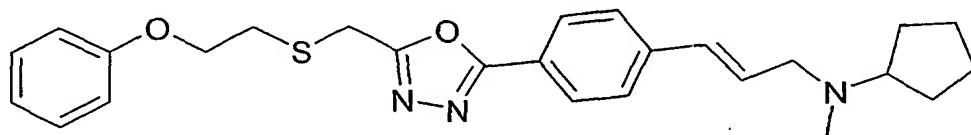
-558-

2H), 7.51 (m, 4H), 7.41 (ap t, 2H), 7.35 (ap d, 1H), 7.30-7.24 (m, 2H), 6.95 (ap t, J = 7.4 Hz, 1H), 6.90 (ap d, 2H), 6.63 (d, J = 15.9 Hz, 1H), 6.42 (m, 1H), 4.22 (t, J = 6.1 Hz, 2H), 4.07 (s, 2H), 3.32 (d, J = 6.2 Hz, 2H), 3.13 (d, J = 12.1 Hz, 2H), 3.07 (t, J = 6.2 Hz, 2H), 2.58 (m, 2H), 2.16 (m, 4H). Anal. calcd. for C₃₂H₃₂N₄O₂S: C, 71.61; H, 6.01; N, 10.44.

5 Found: C, 71.10; H, 6.07; N, 10.22.

Example 312

Cyclopentyl-methyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-amine



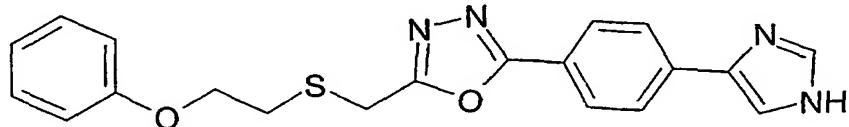
10

The title compound was synthesized from 3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-propenal using a method similar to that described for ethyl-isopropyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-amine: ES-MS 450.3 (M+1), ¹H NMR (CDCl₃): δ 7.97 (ap d, J = 8.3 Hz, 2H), 7.47 (ap d, J = 8.3 Hz, 2H), 7.29-7.24 (m, 2H), 6.95 (ap t, 1H), 6.90 (m, 2H), 6.56 (d, J = 16.1 Hz, 1H), 6.50-6.42 (m, 1H), 4.22 (t, J = 6.1 Hz, 2H), 4.06 (s, 2H), 3.28 (ap d, 2H), 3.05 (t, J = 6.2 Hz, 2H), 2.76 (m, 1H), 2.30 (br s, 3H), 1.90 (m, 2H), 1.73 (m, 2H), 1.64-1.43 (m, 4H). Anal. calcd. for C₂₆H₃₁N₃O₂S: C, 69.46; H, 6.95; N, 9.35. Found: C, 69.24; H, 6.83; N, 9.25.

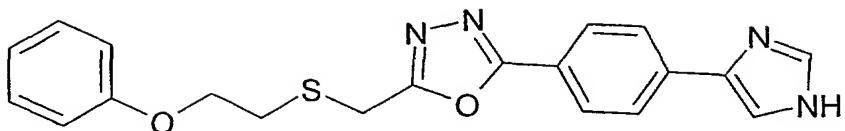
20

Example 313

Preparation of 2-[4-(1H-Imidazol-4-yl)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole



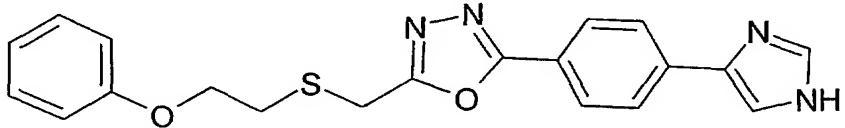
25 a) 2-(2-Phenoxy-ethylsulfanylmethyl)-5-{4-[4-(toluene-4-sulfonyl)-4,5-dihydro-oxazol-5-yl]-phenyl}-[1,3,4]oxadiazole



A solution of 4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzaldehyde (1.53 g, 4.50 mmol) in anhydrous ethanol (10 mL) was treated with tosylmethyl isocyanide (0.70 g, 5.40 mmol) and KCN (0.30 g, 0.45 mmol) and stirred under N₂ at rt for 1 hour, giving a thick slurry.

5 The mixture was diluted with ether and filtered through paper. The precipitate was triturated with ether and filtered again, and the remaining solvent removed under vacuum to give the title compound as an amorphous brown solid:
¹H NMR (CDCl₃): δ 8.06 (ap d, J = 8.4 Hz, 2H), 7.85 (ap d, J = 8.4 Hz, 2H), 7.48 (ap d, J = 8.5 Hz, 2H), 7.39 (ap d, J = 8.0 Hz, 2H), 7.28-7.23 (m, 3H), 6.95-6.87 (m, 3H), 6.12 (d, J = 6.2 Hz, 1H), 5.01 (ap d, J = 6.2 Hz, 1H), 4.21 (t, J = 6.0 Hz, 2H), 4.07 (s, 2H), 3.06 (t, J = 6.0 Hz, 2H), 2.47 (s, 3H).

b) 2-[4-(1H-Imidazol-4-yl)-phenyl]-5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazole



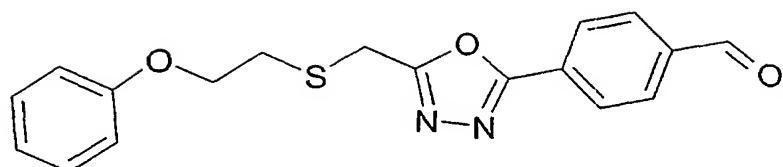
15 In a sealed vial, a solution of 2-(2-Phenoxy-ethylsulfanylmethyl)-5-{4-[4-(toluene-4-sulfonyl)-4,5-dihydro-oxazol-5-yl]-phenyl}-[1,3,4]oxadiazole (0.405 g, 0.75 mmol) in 7N NH₃/MeOH (5 mL, 35 mmol) was microwaved at 100 °C for 15 minutes. The mixture was concentrated, diluted with H₂O, extracted with EtOAc (3 x), dried over MgSO₄, filtered and concentrated. The crude product was purified by radial chromatography on 20 silica gel (gradient EtOAc/Hexane 10%-100%; MeOH/EtOAC 10%) to give the title compound: ES-MS 379.3 (M+1), ¹H NMR (CDCl₃): δ 8.04 (ap d, J = 8.4 Hz, 2H), 7.89 (ap d, J = 8.4 Hz, 2H), 7.82 (s, 1H), 7.46 (s, 1H), 7.29-7.24 (m, 2H), 6.97-6.87 (m, 3H), 4.22 (t, J = 6.1 Hz, 2H), 4.07 (s, 2H), 3.07 (t, J = 6.1 Hz, 2H).

25

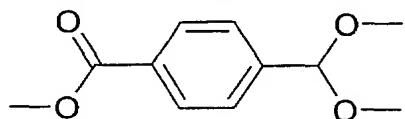
Example 314

Preparation of 4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzaldehyde

-560-

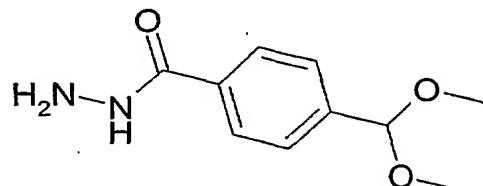


a) 4-Dimethoxymethyl-benzoic acid methyl ester



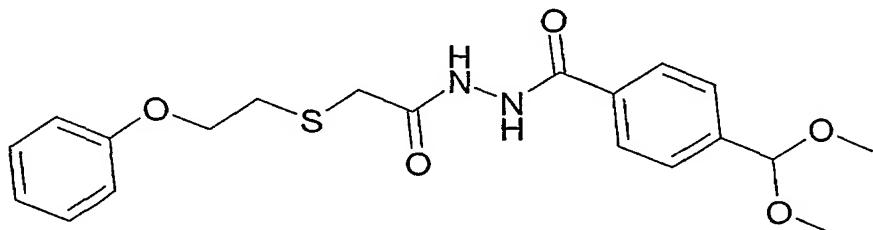
To a solution of 4-formyl-benzoic acid methyl ester (31.9 g, 194 mmol) in methanol (150 mL) was added p-toluenesulfonic acid (36.9 g, 194 mmol), trimethyl orthoformate (42 mL, 388 mmol), and oven-dried 4A mol sieves (20 g). The mixture was stirred at 70 °C for 16 h, concentrated on the Rotovap, diluted with ether, vacuum filtered through paper and the filtrate neutralized with sat. aq. NaHCO₃. The organic phase was set aside, the aqueous phase was extracted with EtOAc (2 x) and the combined organics washed with sat. aq. NaHCO₃, dried over MgSO₄, filtered and concentrated to give the title compound (21.55 g): ¹H NMR (CDCl₃): δ 8.40 (ap d, J = 8.4 Hz, 2H), 7.54 (ap d, J = 8.1 Hz, 2H), 3.93 (s, 3H), 3.34 (s, 6H); TLC (30% EtOAc/Hexane) 0.44.

b) 4-Dimethoxymethyl-benzoic acid hydrazide



To a solution of 4-dimethoxymethyl-benzoic acid methyl ester (21.55 g, 102 mmol) in isopropanol (70 mL) under N₂ was added hydrazine (7.5 mL, 256 mmol) by syringe. The mixture was stirred at 100 °C for 16 hours, allowed to cool to rt and concentrated on the Rotovap. The crude product was redissolved in CH₂Cl₂, concentrated, and placed on high vacuum for 4 hours to give the title compound (21.37 g): ¹H NMR (DMSO-d₆): δ 9.75 (s, 1H), 7.80 (ap d, J = 8.4 Hz, 2H), 7.42 (ap d, J = 8.4 Hz, 2H), 4.51 (br s, 2H), 3.23 (s, 6H); TLC (EtOAc) 0.09.

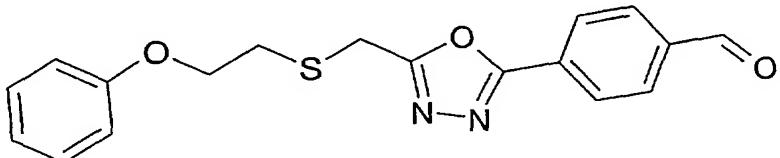
c) 4-Dimethoxymethyl-benzoic acid N'-[2-(2-phenoxy-ethylsulfanyl)-acetyl]-hydrazide



A solution of (2-phenoxy-ethylsulfanyl)-acetic acid (23.83 g, 112 mmol) in THF/MeCN 1:1 (100 mL) was treated with N,N'-carbonyldiimidazole (18.20 g, 112 mmol) then heated at 60 °C for one hour. After cooling to rt, 4-dimethoxymethyl-benzoic acid

- 5 hydrazide (23.60 g, 112 mmol) was added neat. The mixture was stirred for 2 hours at rt, concentrated, diluted with 65% sat. aq. NaHCO₃, extracted with EtOAc (3 x), washed with brine, dried over MgSO₄, filtered, and the solvent removed under vacuum to give the title compound. This crude product was used in the next step without further purification:
 10 ES-MS 387.1 (M+1), ¹H NMR (DMSO-d₆): δ 10.47 (s, 1H), 10.13 (s, 1H), 7.88 (ap d, J = 8.4 Hz, 2H), 7.48 (ap d, J = 8.4 Hz, 2H), 7.29-7.25 (m, 2H), 6.96-6.89 (m, 3H), 4.18 (t, J = 6.6 Hz, 2H), 3.32 (s, 2H), 3.25 (s, 6H), 3.04 (t, J = 6.6 Hz, 2H).

d) 4-[5-(2-Phenoxy-ethylsulfanyl)methyl]-[1,3,4]oxadiazol-2-yl]-benzaldehyde



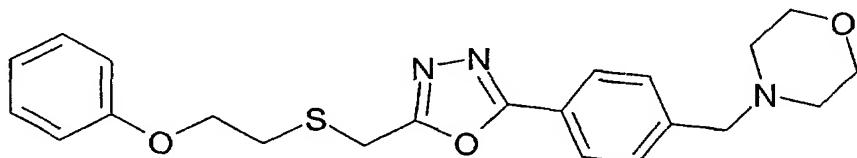
- 15 A mixture of 4-dimethoxymethyl-benzoic acid *N*-[2-(2-phenoxy-ethylsulfanyl)-acetyl]-hydrazide (112 mmol), triphenylphosphine (32.3 g, 123 mmol), and TEA (55 mL, 392 mmol) in THF was chilled in an ice bath and treated with carbon tetrabromide (40.8 g, 331.6 mmol) in 3 portions over 10 minutes. After 30 minutes, the reaction was removed from the bath and stirred 3 hours at rt, then diluted with EtOAc (200 mL) and 2N HCl (250 mL) and stirred overnight. The mixture was poured into EtOAc (200 mL), shaken, and the organic phase removed. The aqueous phase was extracted with EtOAc (2 x) and the combined organic phases were washed with brine, dried over MgSO₄, filtered and concentrated. The resulting crude was purified by flash chromatography on silica gel (gradient EtOAc/Hexane 10%-100%) to give the title compound as a white residue (23.92 g):
 20 ES-MS 341.0 (M+1), ¹H NMR (CDCl₃): δ 10.09 (s, 1H), 8.21 (ap d, J = 8.4 Hz, 2H),
 25

-562-

8.01 (ap d, $J = 8.4$ Hz, 2H), 7.29-7.24 (m, 2H), 6.98-6.87 (m, 3H), 4.23 (t, $J = 6.0$ Hz, 2H), 4.11 (s, 2H), 3.08 (t, $J = 6.0$ Hz, 2H).

Example 315

5 4-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzyl}-morpholine

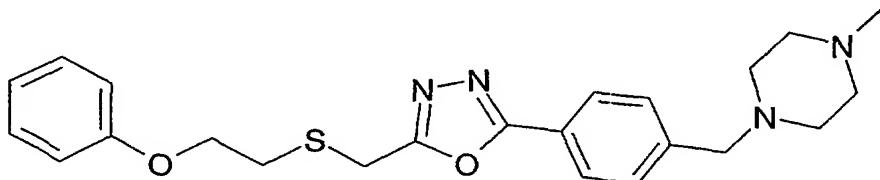


To a solution of 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzaldehyde (0.533 g, 1.57 mmol) in 1,2-dichloroethane (10 mL) was added morpholine (0.27 mL, 3.13 mmol) and finely ground NaBH(OAc)₃ (0.50 g, 2.35 mmol). The reaction
10 was stirred 2 hours at rt, quenched with H₂O (10 mL) and the organic phase removed. The aqueous phase was extracted with EtOAc (2 x) and the combined organic phases dried over MgSO₄, filtered and concentrated. The crude product was purified by flash chromatography on silica gel (gradient EtOAc/Hexane 30%-85%) to give the title compound as an amorphous white solid (0.415 g): ES-MS 412.2 (M+1), ¹H NMR
15 (CDCl₃): δ 7.99 (ap d, $J = 8.4$ Hz, 2H), 7.47 (ap d, $J = 8.4$ Hz, 2H), 7.29-7.24 (m, 2H), 6.95 (ap t, 1H), 6.89 (m, 2H), 4.21 (t, $J = 6.2$ Hz, 2H), 4.06 (s, 2H), 3.73 (t, $J = 4.6$ Hz, 4H), 3.57 (s, 2H), 3.06 (t, $J = 6.2$ Hz, 2H), 2.47 (ap t, 4H). Anal. calcd. for C₂₂H₂₅N₃O₃S: C, 64.21; H, 6.12; N, 10.21; O, 11.66; S, 7.79. Found: C, 64.84; H, 5.86; N, 9.15; O, 11.39; S, 7.99.

20

Example 316

1-Methyl-4-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzyl}-piperazine



25 The title compound was synthesized from 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzaldehyde using a method similar to that described for 4-{4-[5-

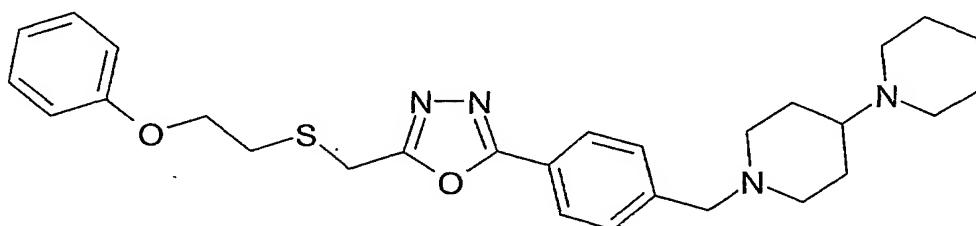
-563-

(2-phenoxy-ethylsulfanyl methyl)-[1,3,4]oxadiazol-2-yl]-benzyl}-morpholine: ES-MS 425.2 (M+1), ¹H NMR (CDCl₃): δ 7.99 (ap d, J = 8.3 Hz, 2H), 7.47 (ap d, J = 8.4 Hz, 2H), 7.30-7.25 (m, 2H), 6.96 (ap t, 1H), 6.90 (m, 2H), 4.22 (t, J = 6.1 Hz, 2H), 4.07 (s, 2H), 3.59 (s, 2H), 3.07 (t, J = 6.1 Hz, 2H), 2.52 (br s, 8H), 2.33 (s, 3H). Anal. calcd. for C₂₃H₂₈N₄O₂S: C, 65.07; H, 6.65; N, 13.20. Found: C, 64.23; H, 6.51; N, 12.96.

5

Example 317

1'-{4-[5-(2-Phenoxy-ethylsulfanyl methyl)-[1,3,4]oxadiazol-2-yl]-benzyl}-[1,4']bipiperidinyl



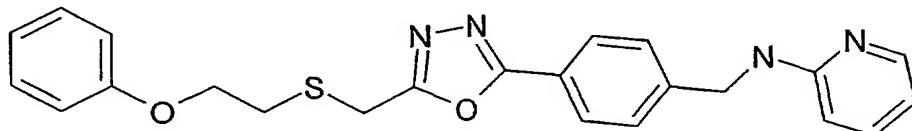
10 The title compound was synthesized from 4-[5-(2-phenoxy-ethylsulfanyl methyl)-[1,3,4]oxadiazol-2-yl]-benzaldehyde using a method similar to that described for 4-{4-[5-(2-phenoxy-ethylsulfanyl methyl)-[1,3,4]oxadiazol-2-yl]-benzyl}-morpholine: ES-MS 493.2 (M+1), ¹H NMR (CDCl₃): δ 7.97 (ap d, J = 8.3 Hz, 2H), 7.45 (ap d, J = 8.3 Hz, 2H), 7.29-7.24 (m, 2H), 6.97-6.88 (m, 3H), 4.21 (t, J = 6.2 Hz, 2H), 4.06 (s, 2H), 3.54 (s, 2H), 3.06 (t, J = 6.2 Hz, 2H), 2.93 (d, J = 11.9 Hz, 2H), 2.53 (br s, 4H), 2.29 (ap t, 1H), 2.00 (ap t, 2H), 1.80 (ap d, 2H), 1.68-1.56 (m, 6H), 1.45 (m, 2H). Anal. calcd. for C₂₈H₃₆N₄O₂S: C, 68.26; H, 7.37; N, 11.37. Found: C, 67.68; H, 7.19; N, 11.22.

15

20

Example 318

{4-[5-(2-Phenoxy-ethylsulfanyl methyl)-[1,3,4]oxadiazol-2-yl]-benzyl}-pyridin-2-yl-amine



25

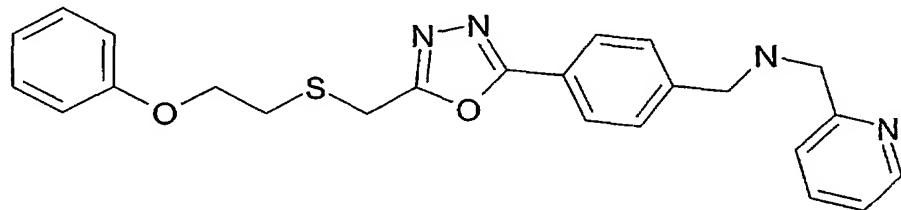
The title compound was synthesized from 4-[5-(2-phenoxy-ethylsulfanyl methyl)-[1,3,4]oxadiazol-2-yl]-benzaldehyde using a method similar to that described for 4-{4-[5-(2-phenoxy-ethylsulfanyl methyl)-[1,3,4]oxadiazol-2-yl]-benzyl}-morpholine: ES-MS

-564-

419.2 (M+1), ¹H NMR (CDCl₃): δ 8.09 (ap d, J = 8.4 Hz, 1H), 8.00 (ap d, J = 8.4 Hz, 2H), 7.51-7.43 (m, 3H), 7.29-7.23 (m, 2H), 6.97-6.87 (m, 3H), 6.65 (m, 1H), 6.41 (ap d, J = 8.3 Hz, 1H), 4.63 (d, J = 6.3 Hz, 2H), 4.21 (t, J = 6.1 Hz, 2H), 4.06 (s, 2H), 3.07 (t, J = 6.2 Hz, 2H). Anal. calcd. for C₂₃H₂₂N₄O₂S: C, 66.01; H, 5.30; N, 13.39. Found: C, 5 65.23; H, 5.36; N, 12.71.

Example 319

{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzyl}-pyridin-2-ylmethyl-amine

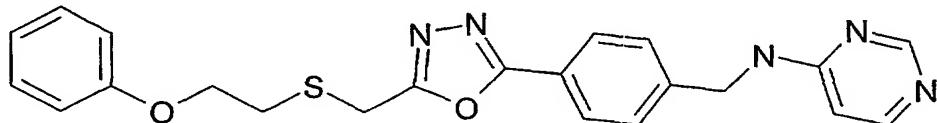


10

The title compound was synthesized from 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzaldehyde using a method similar to that described for 4-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzyl}-morpholine: ES-MS 433.3 (M+1), ¹H NMR (CDCl₃): δ 8.58 (ap d, 1H), 8.00 (ap d, J = 8.2 Hz, 2H), 7.67 (td, J = 7.7, 1.8 Hz, 2H), 7.53 (d, J = 8.4 Hz, 2H), 7.33-7.24 (m, 3H), 7.20 (m, 1H) 6.97-6.88 (m, 3H), 4.22 (t, J = 6.2 Hz, 2H), 4.06 (s, 2H), 3.99 (s, 2H), 3.97 (s, 2H), 3.07 (t, J = 6.2 Hz, 2H).

Example 320

{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzyl}-pyrimidin-4-ylmethyl-amine



The title compound was synthesized from 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzaldehyde using a method similar to that described for 4-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzyl}-morpholine: ES-MS 420.1 (M+1), ¹H NMR (CDCl₃): δ 8.60 (br s, 1H), 8.20 (br s, 1H), 8.00 (ap d, J = 8.3 Hz,

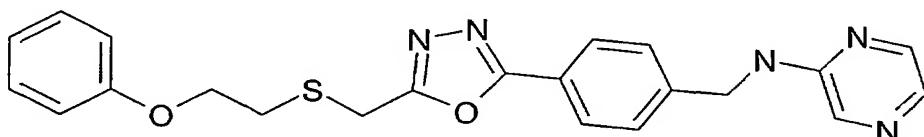
-565-

2H), 7.45 (d, J = 8.2 Hz, 2H), 7.28-7.23 (m, 2H), 6.97-6.86 (m, 3H), 6.37 (d, J = 5.9 Hz, 1H), 4.66 (d, J = 5.9 Hz, 2H), 4.21 (t, J = 6.1 Hz, 2H), 4.06 (s, 2H), 3.06 (t, J = 6.2 Hz, 2H).

5

Example 321

{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzyl}-pyrazin-2-yl-amine

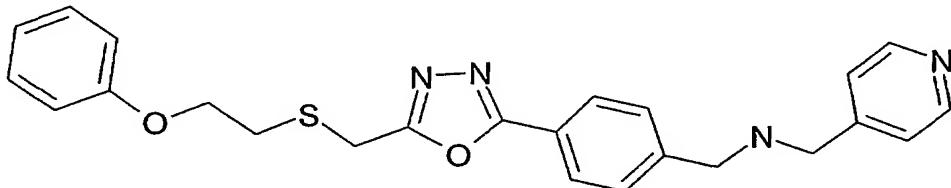


The title compound was synthesized from 4-[5-(2-phenoxy-ethylsulfanylmethyl)-
10 [1,3,4]oxadiazol-2-yl]-benzaldehyde using a method similar to that described for 4-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzyl}-morpholine: ES-MS
420.1 (M+1), ¹H NMR (CDCl₃): δ 8.01-7.83 (m, 5H), 7.46 (d, J = 8.5 Hz, 2H), 7.27-7.22 (m, 2H), 6.95-6.86 (m, 3H), 5.12 (ap t, 1H), 4.66 (d, J = 5.9 Hz, 2H), 4.21 (t, J = 6.1 Hz, 2H), 4.06 (s, 2H), 3.06 (t, J = 6.2 Hz, 2H).

15

Example 322

{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzyl}-pyridin-4-ylmethyl-amine

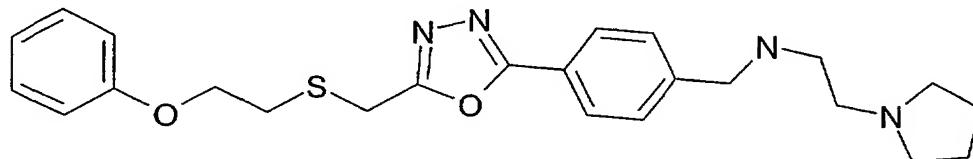


20 The title compound was synthesized from 4-[5-(2-phenoxy-ethylsulfanylmethyl)-
[1,3,4]oxadiazol-2-yl]-benzaldehyde using a method similar to that described for 4-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzyl}-morpholine: ES-MS
433.3 (M+1), ¹H NMR (CDCl₃): δ 8.57 (dd, J = 4.0, 1.5 Hz, 2H), 8.01 (ap d, J = 8.4 Hz, 2H), 7.49 (ap d, J = 8.4 Hz, 2H), 7.32-7.24 (m, 4H), 6.98-6.88 (m, 3H), 4.22 (t, J = 6.1 Hz, 2H), 4.07 (s, 2H), 3.90 (s, 2H), 3.85 (s, 2H), 3.07 (t, J = 6.1 Hz, 2H).

-566-

Example 323

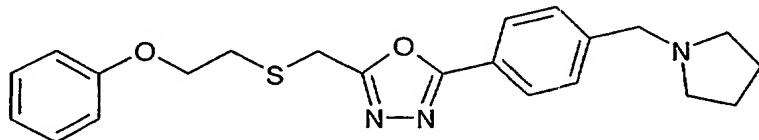
{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzyl}-(2-pyrrolidin-1-yl-ethyl)-amine



- 5 The title compound was synthesized from 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzaldehyde using a method similar to that described 4-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzyl}-morpholine: ES-MS 439.3 (M+1), ^1H NMR (CDCl_3): δ 7.99 (ap d, $J = 8.4$ Hz, 2H), 7.48 (ap d, $J = 8.4$ Hz, 2H), 7.29-7.24 (m, 2H), 6.98-6.88 (m, 3H), 4.22 (t, $J = 6.1$ Hz, 2H), 4.06 (s, 2H), 3.90 (s, 2H), 3.07 (t, $J = 6.1$ Hz, 2H), 2.85-2.60 (m, 6H), 1.83 (m, 6H). Anal. calcd. for $\text{C}_{24}\text{H}_{30}\text{N}_4\text{O}_2\text{S}$: C, 65.72; H, 6.89; N, 12.77; O, 7.30; S, 7.31. Found: C, 65.54; H, 6.91; N, 12.65; O, 7.62; S, 7.31.
- 10

Example 324

- 15 2-(2-Phenoxy-ethylsulfanylmethyl)-5-(4-pyrrolidin-1-ylmethyl-phenyl)-[1,3,4]oxadiazole



The title compound was synthesized from 4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzaldehyde using a method similar to that described 4-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzyl}-morpholine:

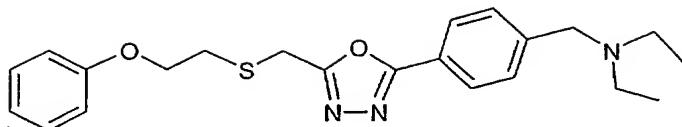
- 20 Exact Mass 395.17: MS (aspci): m/z = 396.2 (M+1); ^1H NMR (CDCl_3 , 300 MHz): δ 8.00 (d, 2H, $J = 7.65$ Hz), 7.47 (d, 2H, $J = 7.60$), 6.28 (app t, 2H, $J = 7.6$ Hz), 6.86-7.00 (m, 3H), 4.23 (t, 2H, $J = 6.3$ Hz), 4.07 (s, 2H), 3.71 (s, 2H), 3.06 (t, 2H, $J = 6.9$ Hz), 2.48-2.62 (m, 4H), 1.75-1.90 (m, 4H). TLC (EtOAc) R_f 0.02.

25

Example 325

Diethyl- {4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzyl}-amine

-567-



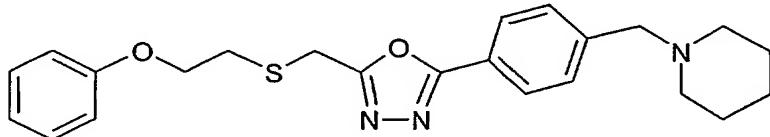
The title compound was synthesized from 4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzaldehyde using a method similar to that described 4-[4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzyl]-morpholine:

- 5 Exact Mass 397.18: MS (aspci): m/z = 398.2 (M+1);
¹H NMR (CDCl₃, 300 MHz): δ 7.99 (d, 2H, J = 7.5 Hz), 7.50 (d, 2H, J = 7.5), 7.27 (t, 3H, J = 7.4 Hz), 6.86-7.00 (m, 4H), 4.22 (t, 2H, 6.0 Hz), 4.07 (s, 2H), 3.07 (t, 2H, J = 6.6 Hz), 2.57 (q, 4H, J = 7.5 Hz), 1.07 (t, 6H, J = 7.0 Hz). TLC (EtOAc) R_f 0.01.

10

Example 326

1-[4-[5-(2-Phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzyl]-piperidine



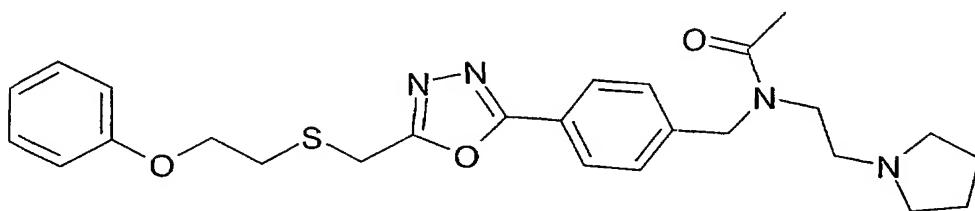
- 15 The title compound was synthesized from 4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzaldehyde using a method similar to that described 4-[4-[5-(2-phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzyl]-morpholine:

Exact Mass 409.18: MS (aspci): m/z = 410.1 (M+1);
¹H NMR (CDCl₃, 300 MHz): δ 7.90-8.10 (m, 2 H), 7.42-7.58 (m, 2H), 7.15-7.45 (m, 3 H), 6.85-7.00 (m, 4 H), 4.22 (t, 2 H, J = 5.95 Hz), 4.07 (s, 2 H), 3.55 (b s, 2H), 3.08 (t, 2H, J = 6.3 Hz), 2.30-2.49 (m, 4 H), 1.38-1.70 (m, 6 H). TLC (EtOAc) R_f 0.02.

20

Example 327

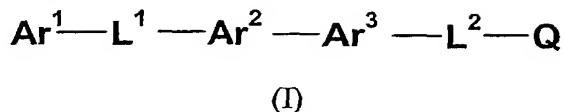
N-[4-[5-(2-Phenoxyethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzyl]-N-(2-pyrrolidin-1-yl-ethyl)-acetamide



A mixture of {4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-benzyl}-(2-pyrrolidin-1-yl-ethyl)-amine (0.505 g, 1.14 mmol) and pyridine (1.8 mL, 23 mmol) in CH₂Cl₂ (8 mL) was treated with acetic anhydride (1.1 mL, 11.4 mmol) and stirred at rt overnight. The mixture was poured into sat. aq. NaHCO₃ and extracted with EtOAc (3 x). The combined organics were dried over MgSO₄, filtered and concentrated. The crude product was purified by radial chromatography (gradient EtOAc/Hexane 20%-100%; 7N NH₃ in MeOH/EtOAc 10%-20%) and recrystallized in CH₂Cl₂/ether/hexane to give the title compound as a white powder (0.288 g): ES-MS 481.3 (M+1), ¹H NMR (CDCl₃): δ 10 8.00 (m, 2H), 7.39-7.24 (m, 4H), 6.98-6.88 (m, 3H), 4.70 (s, 2H), 4.22 (ap t, J = 6.1 Hz, 2H), 4.07 (d, J = 4.3 Hz, 2H), 3.60-3.40 (m, 2H), 3.02 (m, 2H), 2.62 (t, J = 7.5 Hz, 2H), 2.51 (ap t, 4H), 2.24, 2.14 (s, 3H), 1.85-1.76 (m, 4H). Anal. calcd. for C₂₆H₃₂N₄O₃S: C, 64.97; H, 6.71; N, 11.66; O, 9.99; S, 6.67. Found: C, 65.08; H, 6.75; N, 11.70; O, 9.88; S, 6.77.

WE CLAIM:

1. A compound of formula I:



- 5 or a pharmaceutically acceptable salt, solvate, enantiomer, diastereomer or mixture of diastereomers or prodrug thereof wherein:

Ar^1 is a cyclic group optionally substituted with one to five groups selected from C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, hydroxy, C₁-C₈ alkoxy, C₁-C₈ alkylaryl, phenyl, -O-aryl, heteroaryl, cycloalkyl, C₁-C₈ alkylcycloalkyl, cyano, -(CH₂)_nNR⁶R⁶, C₁-C₈ haloalkyl, C₁-C₈ haloalkoxy, halo, (CH₂)_nCOR⁶, (CH₂)_nNR⁵SO₂R⁶, -(CH₂)_nC(O)NR⁶R⁶, heterocyclic, and C₁-C₈ alkylheterocyclic; wherein the cycloalkyl, phenyl, aryl, and heterocyclic substitutents are each optionally substituted with one to three groups selected from hydroxy, C₁-C₈ alkoxyalkyl, C₁-C₈ haloalkoxy, C₁-C₈ alkyl, halo, C₁-C₈ haloalkyl, nitro, cyano, amino, carboxamido, phenyl, aryl, alkylheterocyclic, heterocyclic, and oxo;

L^1 is a bond or a divalent linker having a main chain of 1 to 10 atoms; or represented by the formula X₂-(CR³R⁴)_m-X₃ where X₂ is attached to Ar¹ and X₃ is attached to Ar² wherein R³ and R⁴ are independently selected from a bond, hydrogen, C₁-C₈ alkyl, C₂-C₈ alkylene, C₂-C₈ alkynyl, phenyl, aryl, C₁-C₈ alkylaryl; wherein the alkyl, alkenyl, phenyl, and aryl groups are optionally substituted with one to five substitutents independently selected from oxo, nitro, cyano, C₁-C₈ alkyl, aryl, halo, hydroxy, C₁-C₈ alkoxy, C₁-C₈ haloalkyl, (CH₂)_nC(O)R⁶, and (CH₂)_nCONR⁶R⁶;

X₂ is independently oxygen, -CH, -CONH(CR³R⁴)_m, -NHCO(CR³R⁴)_m, -(CR³R⁴)_m, -CHR⁶, -NR⁵, S, SO, SO₂, -O(CR³R⁴)_m, or -S(CR³R⁴)_m;

X₃ is independently oxygen, -C, -CH, -CHR⁶, -(CR³R⁴)_m, -CONH(CR³R⁴)_m, -NHCO(CR³R⁴)_m, -NR⁵, -NR⁵(CR³R⁴)_m, S, SO(CR³R⁴)_m, SO₂(CR³R⁴)_m, S(CR³R⁴)_m, SO, or SO₂; -O(CR³R⁴)_m, or -S(CR³R⁴)_m;

Ar² is a 5-member monocyclic aromatic group or positional isomer thereof, having 1, 2, or 3 heteroatoms independently selected from nitrogen, oxygen and sulfur; and optionally substituted with one to three substitutents selected from C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, hydroxy, C₁-C₈ alkoxy, C₁-C₈ alkylaryl, phenyl, aryl, C₃-C₈

cycloalkyl, C₁-C₈ alkylcycloalkyl, cyano, C₁-C₈ haloalkyl, halo, (CH₂)_nC(O)R⁶, (CH₂)_nC(O)OR⁶, (CH₂)_nNR⁵SO₂R⁶, (CH₂)_nC(O)NR⁶R⁶, and C₁-C₈ alkylheterocyclic; Ar³ is a 6-member monocyclic, aromatic, carbocyclic or heterocyclic ring having 0, 1, 2, or 3 heteroatoms selected from nitrogen, oxygen and sulfur and which is optionally

5 substituted with one to three substituents independently selected from C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, halo, -NHR⁵, C₁-C₈ haloalkyl, C₃-C₈ cycloalkyl, hydroxy, alkoxy, (CH₂)_nC(O)R⁶, (CH₂)_nC(O)OR⁶, (CH₂)_nNR⁵SO₂R⁶, (CH₂)_nC(O)NR⁶R⁶, phenyl, C₁-C₈ alkylaryl, and aryl;

10 L² is a divalent linker having a chain length of between 1 and 10 atoms in the main chain or is represented by the formula:

X₄-(CR³R⁴)_m-X₅;

wherein X₄ is attached to Ar³ and is selected from the group consisting of C, -CH, CHR⁶, -CO, O, -NR⁵, -NC(O)-, -NC(S), -C(O)NR⁵-, -NR⁶'C(O)NR⁶, -NR⁶'C(S)NR⁶, -SO₂NR⁷, -NRSO₂R⁷, and -NR⁶'C(NR⁵)NR⁶;

15 X₅ is selected from the group consisting of -CH₂, -CH, -O(CR³R⁴)_m, NR³(CR³R⁴)_m, SO, SO₂, S, and SCH₂; wherein the group X₄-(CR³R⁴)_m-X₅ imparts stability to the compound of formula (1) and may be a saturated or unsaturated chain or divalent linker.

Q is a basic group or a group represented by -NR¹R²; wherein

R¹ and R² are independently hydrogen, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₃-C₈ cycloalkane, C₁-

20 C₈ alkylaryl, -C(O)C₁-C₈ alkyl, -C(O)OC₁-C₈ alkyl, C₁-C₈ alkylcycloalkane, (CH₂)_nC(O)OR⁵, (CH₂)_nC(O)R⁵, (CH₂)_nC(O)NR⁶R⁶, and (CH₂)_nNSO₂R⁵; wherein each of the alkyl, alkenyl, aryl are each optionally substituted with one to five groups

independently selected from C₁-C₈ alkyl, C₂-C₈ alkenyl, phenyl, and alkylaryl; and

wherein R¹ and R² may combine together, and with the nitrogen atom to which they are

25 attached or with 0, 1, 2 or 3 atoms adjacent to the nitrogen atom to form a nitrogen containing heterocycle which may have 1, or 2 substituents independently selected from C₁-C₈ alkyl, C₂-C₈ alkenyl, C₃-C₈ cycloalkane, C₁-C₈ alkylaryl, -C(O)C₁-C₈ alkyl, -C(O)OC₁-C₈ alkyl, C₁-C₈ alkylcycloalkane, oxo, halo amino, and (CH₂)_nC(O)NR⁶R⁶; provided that L²-Q is not CONH₂; wherein R¹ and R² may combine with the nitrogen

30 atom to which they are attached to form an imine; and provided that Q is not a substituent on an amide;

R^5 is hydrogen, CN, C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_5 - C_8 alkylaryl, $(CH_2)_nNSO_2C_1$ - C_8 alkyl, $(CH_2)_nNSO_2$ phenyl, $(CH_2)_nNSO_2$ aryl, - $C(O)C_1$ - C_8 alkyl, or - $C(O)OC_1$ - C_8 alkyl; and

R^6 and $R^{6'}$ are each independently hydrogen, C_1 - C_8 alkyl, phenyl, aryl, C_1 - C_8 alkylaryl, or C_3 - C_8 cycloalkyl;

- 5 R^7 is hydrogen, C_1 - C_8 alkyl, phenyl, aryl, C_1 - C_8 alkylaryl, or C_3 - C_8 cycloalkyl, and wherein m is an integer from 1 to 8; and n is an integer from 0 to 8.

2. A compound according to Claim 1 wherein the Ar^1 is selected from the group consisting of cycloheptane, cyclohexane, cyclopentane, phenyl, napthyl, benzofuranyl and benzothienyl.

10 3. A compound according to Claim 1 wherein the Ar^1 is selected from the group consisting of phenyl, napthyl, benzofuranyl and benzothienyl.

15 4. A compound according to Claim 1 wherein the group L^1 is a divalent linker selected from the group consisting of: $-CH_2CH_2CH_2-$, $-SCH_2-$, $-OCH_2-$, $-CH_2SCH_2-$, $-CH_2OCH_2-$, $-OCH_2CH_2SCH_2-$, $-O(CH_2)_3SCH_2-$, $-OCH_2CH_2OCH_2-$, $-O(CH_2)_3OCH_2-$, $-O(CH_2)_3CH_2O-$, $-(CH_2)_3SCH_2-$, and $-(CH_2)_4SCH_2-$.

20 5. A compound according to Claim 3 wherein the group L^1 is a divalent linker selected from the group consisting of: $-CH_2SCH_2-$, $-CH_2OCH_2-$, $-OCH_2CH_2OCH_2-$, and $-OCH_2CH_2SCH_2-$.

25 6. A compound according to Claim 1 wherein Ar^2 is a 5-member aromatic group selected from the group consisting of: furan, thiophene, pyrrole, thiazole, oxazole, isoxazole, isothiazole, thiadiazole and oxadiazole.

30 7. A compound according to Claim 5 wherein Ar^2 is a 5-member aromatic group selected from the group consisting of: furan, thiophene, pyrrole, thiazole, oxazole, isoxazole, isothiazole, thiadiazole and oxadiazole.

8. A compound according to Claim 5 wherein Ar² is 5-member aromatic group selected from the group consisting of: furan, oxazole, and oxadiazole.

9. A compound of Claim 1 wherein Ar³ is a 6-member aromatic group
5 selected from the group consisting of phenyl, and pyridine.

10. A compound of Claim 1 wherein Ar³ is 1,4 -phenylene.

11. A compound of Claim 7 wherein Ar³ is 1,4 -phenylene.

10 12. A compound according to Claim 7 wherein Ar³ is pyridine.

13. A compound according to Claim 1 wherein the linker L² is: –
OCH₂CH₂-, -O(CH₂)₃-, -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, -CH=CHCH₂-, -
15 CH=CHCH₂CH₂-, - CH=CHCH₂CH₂CH₂-, -CONHCH₂CH₂CH₂-, -CONHCH₂CH₂-, -
NHCONHCH₂CH₂-, -NHCON(CH₃)CH₂CH₂-, - NHCON(CH₃)CH₂CH₂CH₂-, -
NHCONHCH₂CH₂CH₂-, -NHCSNHCH₂CH₂-, -NHCSNHCH₂CH₂CH₂-, -
NHC(CN)NHCH₂CH₂-, -NHC(CN)NHCH₂CH₂CH₂-, -NHCOCH₂CH₂-, and -
NHCOCH₂CH₂CH₂-.

20 14. A compound according to Claim 5 wherein the linker L² is: –
OCH₂CH₂-, -O(CH₂)₃-, -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, -CH=CHCH₂-, -
CH=CHCH₂CH₂-, - CH=CHCH₂CH₂CH₂-, -CONHCH₂CH₂CH₂-, -CONHCH₂CH₂-, -
15 NHCONHCH₂CH₂-, -NHCON(CH₃)CH₂CH₂-, - NHCON(CH₃)CH₂CH₂CH₂-, -
NHCONHCH₂CH₂CH₂-, -NHCSNHCH₂CH₂-, -NHCSNHCH₂CH₂CH₂-, -
25 NHC(CN)NHCH₂CH₂-, -NHC(CN)NHCH₂CH₂CH₂-, -NHCOCH₂CH₂-, and -
NHCOCH₂CH₂CH₂-.

15. A compound according to Claim 7 wherein the linker L² is: –
30 OCH₂CH₂-, -O(CH₂)₃-, -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, -CH=CHCH₂-, -
CH=CHCH₂CH₂-, - CH=CHCH₂CH₂CH₂-, -CONHCH₂CH₂CH₂-, -CONHCH₂CH₂-, -
NHCONHCH₂CH₂-, -NHCON(CH₃)CH₂CH₂-, - NHCON(CH₃)CH₂CH₂CH₂-, -

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NHCONHCH₂CH₂CH₂-,-NHCSNHCH₂CH₂-,-NHCSNHCH₂CH₂CH₂-,-
NHC(CN)NHCH₂CH₂-,-NHC(CN)NHCH₂CH₂CH₂-,-NHCOCH₂CH₂-,-
NHCOCH₂CH₂CH₂-.

5 16. A compound according to Claim 11 wherein the linker L² is: -
OCH₂CH₂-,-O(CH₂)₃-,-CH₂-,-CH₂CH₂-,-CH₂CH₂CH₂-,-CH=CHCH₂-,-
CH=CHCH₂CH₂-,-CH=CHCH₂CH₂CH₂-,-CONHCH₂CH₂CH₂-,-CONHCH₂CH₂-,-
NHCONHCH₂CH₂-,-NHCON(CH₃)CH₂CH₂-,-NHCON(CH₃)CH₂CH₂CH₂-,-
NHCONHCH₂CH₂CH₂-,-NHCSNHCH₂CH₂-,-NHCSNHCH₂CH₂CH₂-,-
10 NHC(CN)NHCH₂CH₂-,-NHC(CN)NHCH₂CH₂CH₂-,-NHCOCH₂CH₂-,-
NHCOCH₂CH₂CH₂-.

15 17. A compound according to Claim 11 wherein the linker L² is: -
OCH₂CH₂-,-O(CH₂)₃-.

18. A compound according to Claim 11 wherein the linker L² is: -
CH=CHCH₂-,-CH=CHCH₂CH₂-,-CH=CHCH₂CH₂CH₂-.

20 19. A compound according to Claim 11 wherein the linker L² is: -
NHCONHCH₂CH₂-,-NHCON(CH₃)CH₂CH₂-,-NHCON(CH₃)CH₂CH₂CH₂-,-
NHCONHCH₂CH₂CH₂-.

25 20. A compound according to Claim 1 wherein R¹ and R² combine
with the nitrogen atom to form piperidinyl, pyrrolidinyl, azepine, or azetidinyl.

21. A compound according to Claim 1 wherein R¹ and R² are
independently selected from the group consisting of hydrogen, methyl, ethyl, propyl,
isopropyl, methylcyclopentane, methylcyclohexane, phenyl, benzyl, cyclopentyl,
cyclohexyl, methylcyclopropane and methylcyclobutane.

30 22. A compound according to Claim 1 wherein the group Ar² is
oxadiazole.

23. A compound according to Claim 1 wherein the group Ar² is oxazole.

5 24. A compound according to Claim 9 wherein the group Ar³ is phenyl or pyridyl substituted with 1 to 3 substituents selected from chloro, fluoro, trifluoromethyl, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₂-C₈ alkenyl, substituted or unsubstituted phenyl, aryl, C₁-C₈ alkylaryl, (CH₂)_nC(O)R⁶, (CH₂)_nCONR⁶R⁶, and (CH₂)_nOR⁶.

10 25. A compound according to Claim 1 wherein at least one of L¹ and L² has a chain length of between 3 to 8 atoms.

15 26. A compound according to Claim 1 wherein L² has a chain length of between 3 to 8 atoms.

27. A compound selected from the group consisting of:
1-{4-[2-(Benzofuran-2-ylmethoxymethyl)-oxazol-5-yl]-phenyl}-3-(2-dimethylaminoethyl)-urea,

1-{4-[2-(Benzofuran-2-ylmethoxymethyl)-oxazol-5-yl]-phenyl}-3-(2-pyrrolidin-1-ylethyl)-urea,

1-{4-[2-(Benzofuran-2-ylmethoxymethyl)-oxazol-5-yl]-phenyl}-3-(2-piperidin-1-ylethyl)-urea,

1-(3-{4-[5-(Benzofuran-2-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-piperidine,

25 Cyclohexyl-ethyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-amine,

4-(3-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-morpholine,

1-(3-{4-[2-(2-Phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenoxy}-propyl)-azepane,

30 Diethyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-amine,

- 1-(3-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-piperidine,
- (3-{2-Chloro-4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine,
- 5 1-Methyl-4-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-piperazine,
- (3-{2-Fluoro-4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine,
- Ethyl-isopropyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-amine,
- 10 Cyclopentyl-methyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-amine,
- 1-(3-{4-[2-(2-Phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenoxy}-propyl)-azocane,
- Diethyl-(2-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenoxy}-ethyl)-amine,
- 15 Dimethyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-allyl)-amine,
- Dimethyl-(3-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-4-yl]-phenoxy}-propyl)-amine,
- 2-{4-[2-(1-Methyl-pyrrolidin-2-yl)-ethoxy]-phenyl}-5-(2-phenoxy-ethylsulfanylmethyl)-
- 20 [1,3,4]oxadiazole,
- 2-(2-Phenoxy-ethylsulfanylmethyl)-5-[4-(3-pyrrolidin-1-yl-propenyl)-phenyl]-[1,3,4]oxadiazole,
- Dimethyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-furan-2-yl]-phenoxy}-propyl)-amine,
- 4-Dimethylamino-N-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-butyramide,
- 25 1-(2-Dimethylamino-ethyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea,
- 1-(3-Dimethylamino-propyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea,
- 30 Dimethyl-(2-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-ethyl)-amine,

- 1-(2-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-ethyl)-piperidine,
- Dimethyl-(5-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-pent-4-enyl)-amine,
- 5 2-(2-Dimethylamino-ethoxy)-N-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-acetamide,
- Dimethyl-(4-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-butyl)-amine,
- 10 1-(3-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-piperidine,
- Diethyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine,
- 1-(4-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-butyl)-piperidine,
- 15 2-(2-Phenoxy-ethylsulfanylmethyl)-5-[4-(4-pyrrolidin-1-yl-butoxy)-phenyl]-[1,3,4]oxadiazole,
- 1-(3-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-azepane,
- 1-(2-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-ethyl)-azepane,
- 20 Methyl-(3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine,
- Diethyl-(2-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-ethyl)-amine,
- 25 1-(2-Dimethylamino-ethyl)-1-methyl-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea,
- 2-(2-Phenoxy-ethylsulfanylmethyl)-5-[4-(3-pyrrolidin-1-yl-propoxy)-phenyl]-[1,3,4]oxadiazole,
- 1-(5-Dimethylamino-pentyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea,
- 30 1-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-3-(2-piperidin-1-yl-ethyl)-urea,

- 1-(4-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-butyl)-azepane,
- Diethyl-(4-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-butyl)-amine,
- 5 1-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-3-(2-pyrrolidin-1-yl-ethyl)-urea,
- 1-(2-Dimethylamino-ethyl)-3-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea,
- (3-{4-[5-(Benzofuran-2-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine,
- 10 2-(2-Phenoxy-ethylsulfanylmethyl)-5-[4-(5-pyrrolidin-1-yl-pent-1-enyl)-phenyl]-[1,3,4]oxadiazole,
- 1-(5-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-pent-4-enyl)-piperidine,
- 15 1-(3-{4-[5-(2-Phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-piperidin-4-one,
- 2-(2-Phenoxy-ethylsulfanylmethyl)-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-oxazole,
- Dimethyl-(2-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenoxy}-ethyl)-amine,
- 1-(2-{4-[2-(2-Phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenoxy}-ethyl)-piperidine,
- 20 1-(3-{4-[2-(2-Phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenoxy}-propyl)-piperidine,
- 2-(2-Phenoxy-ethylsulfanylmethyl)-5-[4-(3-pyrrolidin-1-yl-propoxy)-phenyl]-oxazole,
- Dimethyl-(3-{4-[2-(2-phenoxy-ethylsulfanylmethyl)-oxazol-5-yl]-phenoxy}-propyl)-amine,
- Dimethyl-(6-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-hex-5-enyl)-amine,
- 25 Dimethyl-(4-{4-[5-(2-phenoxy-ethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-but-3-enyl)-amine,
- Dimethyl-(3-{4-[4-(2-phenoxy-ethylsulfanylmethyl)-thiazol-2-yl]-phenoxy}-propyl)-amine,
- 30 (3-{4-[5-(Benzo[b]thiophen-2-ylmethylsulfanylmethyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-dimethyl-amine,

Dimethyl-(3-{4-[5-(naphthalen-2-ylmethylsulfanyl methyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine,

Dimethyl-(3-{4-[5-(2-phenoxy-ethylsulfanyl methyl)-[1,3,4]oxadiazol-2-yl]-phenoxy}-propyl)-amine,

5 2-(2-Phenoxy-ethylsulfanyl methyl)-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-[1,3,4]oxadiazole,

2-[4-(3-Azetidin-1-yl-propoxy)-phenyl]-5-(2-phenoxy-ethylsulfanyl methyl)-[1,3,4]oxadiazole,

10 1-{4-[2-(2-Phenoxy-ethylsulfanyl methyl)-oxazol-5-yl]-phenyl}-3-(2-piperidin-1-yl-ethyl)-urea,

1-{4-[2-(2-Phenoxy-ethylsulfanyl methyl)-oxazol-5-yl]-phenyl}-3-(2-pyrrolidin-1-yl-ethyl)-urea,

1-(2-Dimethylamino-ethyl)-3-{4-[2-(2-phenoxy-ethylsulfanyl methyl)-oxazol-5-yl]-phenyl}-urea,

15 1-(2-Dimethylamino-ethyl)-3-{4-[2-(2-phenoxy-ethylsulfanyl methyl)-oxazol-5-yl]-phenyl}-urea,

1-{4-[2-(2-Phenoxy-ethylsulfanyl methyl)-oxazol-5-yl]-phenyl}-3-(3-pyrrolidin-1-yl-propyl)-urea,

20 1-{4-[5-(2-Phenoxy-ethylsulfanyl methyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-3-(3-pyrrolidin-1-yl-propyl)-urea,

N,N-dimethyl-N'-{5-[5-(2-phenoxy-ethylsulfanyl methyl)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-ethane-1,2-diamine,

N,N-Dimethyl-N'-{5-[5-(2-phenoxy-ethylsulfanyl methyl)-[1,3,4]oxadiazol-2-yl]-pyridin-2-yl}-propane-1,3-diamine,

25 1-Methyl-3-{4-[5-(2-phenoxy-ethylsulfanyl methyl)-[1,3,4]oxadiazol-2-yl]-phenoxy methyl}-piperidine,

2-(2-Phenoxy-ethylsulfanyl methyl)-5-[4-(3-pyrrolidin-1-yl-propenyl)-phenyl]-oxazole,

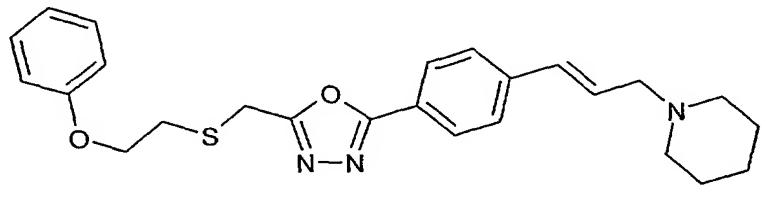
1-(2-Diethylamino-ethyl)-3-{4-[5-(2-phenoxy-ethylsulfanyl methyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-urea,

30 5-(2-Phenoxy-ethylsulfanyl methyl)-3-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-[1,2,4]oxadiazole,

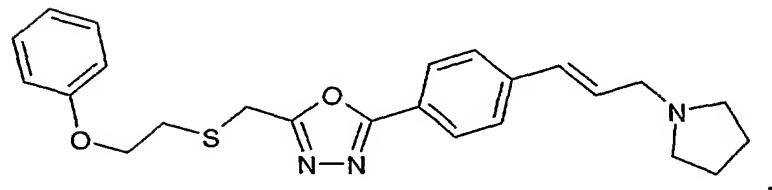
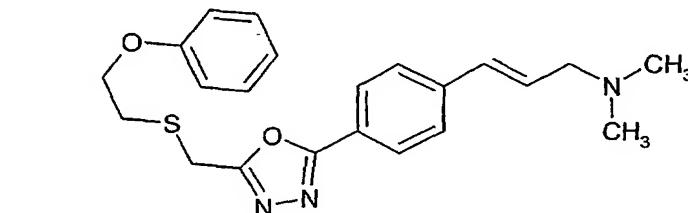
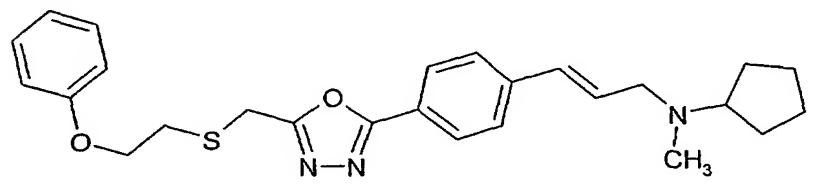
Dimethyl-(2-{4-[5-(2-phenoxy-ethylsulfanyl-methyl)-[1,2,4]oxadiazol-3-yl]-phenoxy}-ethyl)-amine, and pharmaceutically acceptable salts, solvates, enantiomers, diastereomers and mixture of diastereomers thereof.

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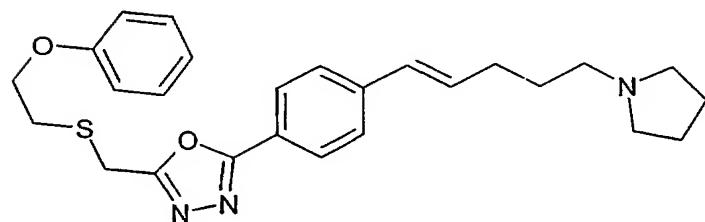
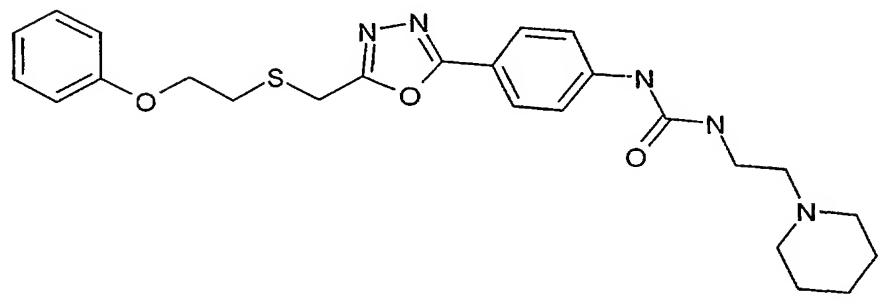
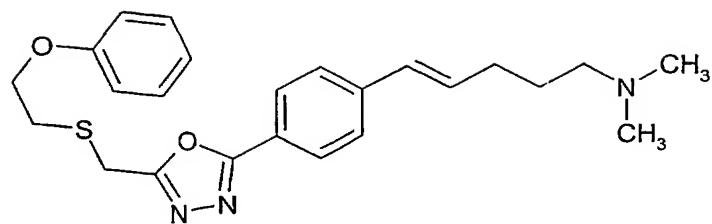
28. A compound represented by the formulae.



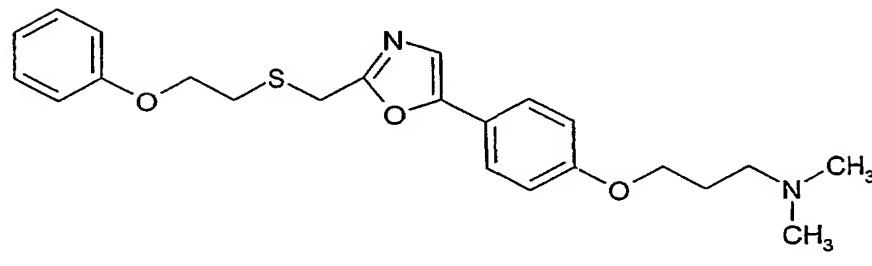
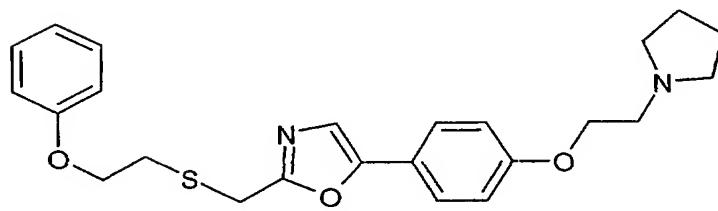
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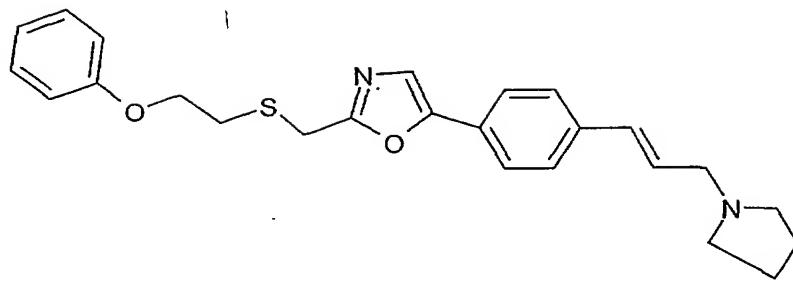


-580-



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or a pharmaceutically acceptable salt, solvate, prodrug, enantiomer, diasteromer or mixture of diastereomers thereof.

5 29. The compound of any one of Claims 1-28 which is the hydrochloride salt or the bisulfate salt.

30. A method of treating obesity comprising administering to a patient in need thereof a compound of any one of Claims 1-28.

10 31. A method of preventing Type II Diabetes comprising administering to a patient in need thereof a compound of any one of Claims 1-28.

15 32. A method of inhibiting release of the melanocortin concentrating hormone comprising administering to a patient in need thereof a compound of any one of Claims 1-28.

33. A method of treating, preventing or ameliorating the symptoms of obesity and Related Diseases comprising administering to a patient in need thereof, a pharmaceutically effective amount of a compound of formula I.

20 34. A pharmaceutical formulation comprising a compound of any one of Claims 1-28 and a pharmaceutical carrier for the treatment of obesity and related diseases.

25 35. Use of a compound of formula I as an appetite suppressant.

36. Use of a compound of formula I for the treatment, prevention or amelioration of the symptoms of eating disorders (bulima, anorexia nervosa, etc.), diabetes, diabetic complications, diabetic retinopathy, sexual/reproductive disorders, depression, anxiety, social withdrawal, urge incontinence, epileptic seizure, hypertension, 5 cerebral hemorrhage, congestive heart failure, sleeping disorders, atherosclerosis, rheumatoid arthritis, stroke, hyperlipidemia, hypertriglyceridemia, hyperglycemia, and hyperlipoproteinemia, comprising administering an effective amount of a compound of formula I to a patient in need thereof.
- 10 37. Use of a compound of formula I in the manufacture of a medicament for the treatment of obesity and Related Diseases including diabetes mellitus, hyperglycemia, obesity, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, atherosclerosis of coronary, cerebrovascular and peripheral arteries, gastrointestinal disorders including peptid ulcer, esophagitis, gastritis and duodenitis, (including that 15 induced by H. pylori), intestinal ulcerations (including inflammatory bowel disease, ulcerative colitis, Crohn's disease and proctitis) and gastrointestinal ulcerations, neurogenic inflammation of airways, including cough, asthma, depression, prostate diseases such as benign prostate hyperplasia, irritable bowel syndrome and other disorders needing decreased gut motility, diabetic retinopathy, neuropathic bladder dysfunction, 20 elevated intraocular pressure and glaucoma and non-specific diarrhea dumping syndrome.
38. The combination of a compound of formula I, its salt, enantioner or prodrug thereof, with other approved therapeutic agents for the treatment and/or prevention of obesity and related diseases.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/12123

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/4245	A61K31/422	A61P3/04	C07D271/10	C07D413/12
C07D263/32	C07D277/26	C07D413/06	C07D333/18	C07D249/08
C07D413/14	C07D417/12	C07D413/04	C07D413/10	C07D261/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02 10146 A (JOHNSON CHRISTOPHER NORBERT ;THEWLIS KEVIN MICHAEL (GB); WITTY DAV) 7 February 2002 (2002-02-07) page 2, line 8 - line 22; claim 1 ---	1-38
X	WO 02 32897 A (PFIZER PROD INC ;DAY ROBERT FRANCIS (US); LAFONTAINE JENNIFER ANNE) 25 April 2002 (2002-04-25) 2nd compound of claims 3 and 17 claims 1,3,6,16,17 ---	1-38
X	US 6 034 106 A (FENG DANQING DENNIS ET AL) 7 March 2000 (2000-03-07) claims 1,3,4 ---	1-38
X	US 3 708 598 A (GRIOT R) 2 January 1973 (1973-01-02) claim 1; example 1 ---	1-38
	-/-	

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

° Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

21 July 2003

Date of mailing of the international search report

05/08/2003

Name and mailing address of the ISA

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Authorized officer

Johnson, C

INTERNATIONAL SEARCH REPORT

International	ation No
PCT/US 03/12123	

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D271/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	GALLAGHER T F ET AL: "Regulation of stress -induced cytokine production by pyridinylimidazoles; inhibition of CSBP kinase" BIOORGANIC & MEDICINAL CHEMISTRY, ELSEVIER SCIENCE LTD, GB, vol. 5, no. 1, 1997, pages 49-64, XP002094123 ISSN: 0968-0896 table 5 ---- ----	1,9,10, 13,21, 25,26

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

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Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/12123

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DIWU Z ET AL: "FLUORESCENT MOLECULAR PROBES II. THE SYNTHESIS, SPECTRAL PROPERTIES AND USE OF FLUORESCENT SOLVATOCHROMIC DAPOXYL DYES" PHOTOCHEMISTRY AND PHOTOBIOLOGY, OXFORD, GB, vol. 66, no. 4, 1997, pages 424-431, XP009003751 ISSN: 0031-8655 examples 12,13,16-19,21,22 ---	1-3,6,9, 10,21, 23,25,26
X	US 2 641 601 A (ISRAEL RACHLIN ALBERT ET AL) 9 June 1953 (1953-06-09) claims 1-4,6; examples 12,13 ---	1-3,6,9, 10,13, 21,25,26
X	NI W ET AL: "SYNTHESIS AND LUMINESCENT PROPERTIES OF 2-PHENYL-5-{4' 2-(6-SUBSTITUENT-2H-BENZ'DE! ISOQUINOLINE-1,3(2H)-DIONE-2-YL)POLYMETHANO-!AMINO-{PHENYL-1,3,4-OXADIAZOLE" CHEMISTRY LETTERS, CHEMICAL SOCIETY OF JAPAN. TOKYO, JP, no. 1, 1997, pages 101-102, XP000671632 ISSN: 0366-7022 page 101, right-hand column, line 1,2 ---	1-3,6,9, 10,13, 21,22
X	DE LASZLO S E ET AL: "Pyrroles and other heterocycles as inhibitors of P38 kinase" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 8, no. 19, 6 October 1998 (1998-10-06), pages 2689-2694, XP004139602 ISSN: 0960-894X examples 47,48 ---	1-3,6,9, 10,13, 20,25,26
X	MCLAY, I.M. ET AL.: "The discovery of RPR 200765A, a p38 MAP kinase inhibitor displaying a good oral anti-arthritic efficacy" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 9, 2001, page 537-554 XP002248371 OXFORD, GB table 5 --- -/-	1-3,13, 21

INTERNATIONAL SEARCH REPORT

Internatio

cation No

PCT/US 03/12123

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MEYER, H-J, ET AL.: "Water-binding solid scintillators: synthesis, emission properties, and tests in ³ H and ¹⁴ C counting" CHEM. EUR. J., vol. 6, no. 15, 2000, pages 2809-2817, XP002248372 WEINHEIM, DE example 7 ---	1-3,6,9, 10,13, 21,23
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. BRN 567765 XP002248373 abstract & SHEVCHENKO, L.I. ET AL.: SOV. PROG. CHEM. (ENGL. TRANSL.), vol. 44, no. 8, 1978, pages 58-61, ---	1-3,6,9, 10,13,21
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. BRN 6936668 XP002248374 abstract & LITAK, P. ET AL.: J. HETEROCYCL. CHEM., vol. 31, no. 2, 1994, pages 457-480, ---	1-3,6,9, 10,21, 23,25,26
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. BRN 1507962, 1502375, 1512417 XP002248375 abstract & IYER & GOPALACHARI: INDIAN J. CHEM., vol. 11, 1973, page 1260 ---	1-3,6,9, 10,13, 21,25,26
X	GOFF D ET AL: "The Preparation of 2,4-Disubstituted Thiazoles on Solid Support" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 40, no. 3, 15 January 1999 (1999-01-15), pages 423-426, XP004151347 ISSN: 0040-4039 table 2 ---	1-4,6,9, 10,25,26

-/-

INTERNATIONAL SEARCH REPORT

International

Location No

PCT/US U3/12123

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2 858 318 A (WILFRIED GRAF ET AL) 28 October 1958 (1958-10-28) table I ---	1-4,6,9, 10,21,25
X	PENNING ET AL: "Synthesis and Biological Evaluation of the 1,5-Diarylpyrazole Class of Cyclooxygenase-2 Inhibitors: Identification of 4-'5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl!benzene-sulfonamide (SC-58635, Celecoxib)" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 40, 1997, pages 1347-1365, XP002114833 ISSN: 0022-2623 examples 15A,12A -----	1-5,9, 10,21,25

INTERNATIONAL SEARCH REPORT

Interr. application No.
PCT/US 03/12123

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 30–33, 35–37 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: 1–26 (part), 28–38 (part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-26 (part), 28-38 (part)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). The documents cited in the International Search Report are merely a selection of those found. For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible. Consequently, a complete search has only been performed for compounds of formula (I) having the groups Ar1, Ar2, Ar3, L1, L2 and Q which are illustrated in claim 27.

Present claims 1, 28 and 38 relate to a compound defined by reference to a desirable characteristic or property, namely prodrugs. The claims cover all compounds having this characteristic or property, whereas the application provides no support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for any such compounds (the term prodrug does not appear to be defined in the application). In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds of formula (I), their salts, solvates, enantiomers and diastereomers.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International

Application No

PCT/US 03/12123

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
WO 0210146	A	07-02-2002	AU BR CA CZ WO EP NO	7850801 A 0112856 A 2417638 A1 20030297 A3 0210146 A1 1305304 A1 20030471 A		13-02-2002 01-07-2003 07-02-2002 14-05-2003 07-02-2002 02-05-2003 28-03-2003
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US 6034106	A	07-03-2000	AU AU CA EP JP WO	712057 B2 3374897 A 2257206 A1 0906310 A1 2000511903 T 9746556 A1		28-10-1999 05-01-1998 11-12-1997 07-04-1999 12-09-2000 11-12-1997
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